INNOVATION AND BUSINESS STRATEGY IN HEALTHCARE MARKETS

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INNOVATION AND BUSINESS STRATEGY IN HEALTHCARE MARKETS

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SUMMARY

In the first chapter, we use patent and financial data from the pharmaceutical industry to examine the effects of international innovation on profitability and the channels through which the effects take place. Positive impacts of internationalization are found for both innovation performance and financial performance. In the second chapter, we examine the impact of uncertainty on firms' decisions related to R&D expenditures, patenting, and physical capital investments using a sample of firms in the global pharmaceuticals industry. Our results indicate that uncertainty has mixed effect on the innovation variables: it affects R&D negatively, but has a weak and ambiguous effect on patents. The estimated impact on capital investment is negative. In the third chapter, using U.S. Food and Drug Administration (FDA) recall data from 2001-2013, we examine various factors that may determine recalls. We consider a wide range of firm-specific and device-specific measures such as their R&D expenditures, foreign versus domestic ownership, size of firms, degree of vertical integration, device complexity, profitability, among several other variables. In our empirical analysis, we examine whether there are systematic longer-run differences in recalled devices across the firms in our sample, and whether firm-specific and device-specific attributes can explain why some firms systematically have a higher or lower number of recalls.

CHAPTER 1. INTERNATIONALIZATION OF INNOVATION, PATENTS, AND FIRM PERFORMANCE IN THE PHARMACEUTICAL INDUSTRY

1.1 Introduction

With the advance of globalization, the number of research and development (R&D) facilities established by firms in foreign locations has been increasing. This has drawn increasing academic and policy attention to examine the determinants and the effects of the internationalization of innovation. Early work of the internationalization of innovation focused on the determinants of international innovation (e.g., Cheng and Bolon, 1993; Granstrand et al. 1993), and the organizational management of international innovation (e.g., Gassmann and von Zedtwitz, 1998; Nobel and Birkinshaw, 1998). In a comprehensive survey of early studies on this topic, Granstrand et al. (1993) summarized forces stimulating internationalization of innovation at company, national, and international levels. Some of the important forces at the firm level include: subsidiaries previously depending on technology transfer from parents might establish their own units to save cost; multinational enterprises might conduct R&D targeted on local needs to better serve local markets; and friendly government policies of developing countries might provide low-cost local R&D personnel. Subsequent studies continued the investigation on the determinants and focused more on the effects of the internationalization of R&D and innovation more generally.

From this literature, it appears that internationalization of innovation could be driven by either the advantages of its home country, or the advantages of the host country. In the first case, a firm can extend its existing innovation competencies to a foreign country and to earn extra overseas profits; in this case it is likely that knowledge flows from the firm's host country to the foreign country. In the second case, a firm can augment its existing knowledge base by tapping into foreign knowledge; in this case, knowledge is likely to flow from the foreign country to the firm. These two channels are often called "exploiting" and "exploring" (He and Wong, 2004).

The benefits from "exploitation" include refining existing knowledge, reducing transaction costs, and expediting decision-making (Özsomer and Gençtürk, 2003). Benefits from "exploration" include tapping into leading knowledge in the host country for new technology, and communicating with local suppliers and customers for new ideas (e.g., Penner-Hahn and Shaver, 2005). Besides these benefits, firms also have to deal with costs associated with internationalization of innovation. These include increase in coordination cost (Singh, 2008), communication cost (Fisch, 2003), possible rent-seeking behavior of subsidiaries (Mudambi and Navarra, 2004), and risk from the uncertainty of the host economic environment and information leakage (Granstrand et al., 1993).

Besides the discussion on the possible benefits and costs of internationalization of innovation, the limited number of studies on the impacts have mixed findings. This paper will add to the literature of the impacts of international innovation on both innovation performance and financial performance. To fully investigate the impacts, we compiled a dataset on top pharmaceutical firms in U.S. and Europe including both financial and innovation data. A comprehensive set of indicators were built to measure different aspects

of the international innovation. Based on the estimation results of the indicators, we can easily find the aspects of the internal innovation contribute most to firms' innovation or financial performance. Therefore, this paper can provide suggestions for firms' strategies in the international innovation.

In next section, we summarize several empirical studies on the effects of internationalization of innovation. In Section 3 we discuss the industry context for our study. In section 4, we discuss the research question and note our hypotheses. Section 5 provides details of our data, and in Section 6 we note our variable definitions, conduct a preliminary data analysis, and specify the estimation strategies. In Section 7 we discuss the estimation results. Section 8 presents our concluding remarks.

1.2 Studies on the Effects of Internationalization of Innovation

Although several studies have suggested that internationalization of innovation can affect firm performance, a somewhat limited number of studies have rigorously empirically explored these effects. The evidence is mixed.

For financial performance, Fors (1997) found that affiliate R&D had no significant influence on parent firm growth, while Todo and Shimizutani (2008) only found weakly positive effects on parent firm productivity. For innovation performance, Penner-Hahn and Shaver (2005) found that international R&D could increase the patents outputs for Japanese pharmaceutical firms with existing research capabilities in the underlying technologies; Furman et al. (2005) found that the number of R&D locations in a specific therapeutic class for U.S. pharmaceutical firms is negatively related to patent counts; Leiponen and Helfat

(2006) found that dispersed R&D in Finnish firms only benefits firms' imitative innovation, and not novel innovation.

Based on the benefits and costs of the internationalization of innovation, we examine its effects on firms' financial performance. Since the effects of internationalization innovation on innovation would finally influence firm's financial performance through its effects on innovation, we also examine the effects of international innovation on innovation outcomes. In this study, we will not treat the two types of performances separately, but analyze them together to better understand the effects of internationalization on firms' innovation and performance.

1.3 Research Question

1.3.1 Industry Context

The main participants of international innovation are firms operating in R&D-intensive industries. Gassmann and von Zedtwitz (1999) studied globally dispersed R&D and relationships between individual R&D sites. They divided firms into five categories in terms of international R&D organization: (1) ethnocentric centralized R&D, (2) geocentric centralized R&D, (3) polycentric decentralized R&D, (4) R&D hub model, and (5) integrated R&D network. Since the pharmaceutical industry has developed systematically towards competence-based organization, they assigned it to the last category, which is characterized by an organizational structure with highly dispersed R&D and several competence R&D centers.

A survey by Dunning and Wymbs (1999) on the world largest multinationals shows an important reason for this categorization – pharmaceutical firms obtain more of their competitive advantage from foreign sources than firms in other sectors. A report by the National Science Board (2012) compared the internationalization of innovation among industries in United States. This study revealed that by 2012, the pharmaceutical industry was the industry that performed the most R&D outside of the United States ($10.9 billion), based on Business R&D and Innovation Survey. Given these facts, the pharmaceutical industry is a good subject for studying international innovation.

As one of the few studies on the effect of internationalization of innovation, the study by Penner-Hahn and Shaver (2005) examined the effect of international R&D on patent output of Japanese pharmaceutical firms. They found that firms benefit from international R&D only when they possess existing research capabilities in the underlying technologies.

Using patent data from three (you say three, but only TWO are mentioned) major patent authorities, EPO (European Patent Office) and USPTO (United States Patent and Trademark Office), this paper examines the dynamics of patenting under the influence of the international innovation and investigates the relationship between international innovation and firm performance of large U.S. and European pharmaceutical firms.

1.3.2 Hypothesis for Testing

According to previous studies (Archibugi and Michie, 1995; Archibugi and Lammarino, 1999), globalization of innovation falls into three categories: (1) the international exploitation of technology produced on a national basis; (2) the technological collaborations of firms across national borders, i.e. agreements between firms for joint

development; (3) the global generation of innovation by MNCs. Since the first category concerns exports of goods, licensing, and production rather that R&D activities, while the second is about two different firms located in two or more countries, we focus on the third category in this study, which refers to innovation generated by single proprietors on the global scale.

As mentioned previously, firms have many motivations to be involved in international innovation. Whether the motivation is more of home country advantage or host country advantage, the expecting results for all these strategies and actions is to apply or improve firms' research capability. For the international innovation driven by home country the firms would extend its existing knowledge to the host country through adapting its existing technology to local market, which would lead to patents of the technology in the host country. The adaptation and feedbacks from the new market would also be beneficial for firms' future innovation, which would reveal as more patents in the future. For the international innovation driven by host country advantage, the results are clearer. The firm would acquire new technologies by accessing the knowledge that is geographically bound in the host country, improve its research capability by learning after local companies and research institutes, and gaining new ideas by communicating with customers form more advanced markets. Therefore, we will first test the following hypothesis:

Hypothesis 1: International innovation is expected to increase the number of patents granted to a firm.

Economists have long explored the impacts fo R&D activities. R&D has been found to beneficial for improvements on productivity (Mansfield, 1980; Griliches, 1986; etc.), which will eventually show in the profit. For the pharmaceutical industry the link between R&D and profit is even clearer. The patents for a new drug would secure the exclusive selling rights for the firm, then leads to extra profit for the firm. Therefore, following the channel of Hypothesis 1, the positive effects of international innovation on innovation output, or patent output, would eventually lead to its positive effects on profit. In addition, there are also other channels through which the international innovation would have impacts on firms' profits. As mentioned above, the other benefits of international innovation, including reducing transaction costs, higher reputation in local market, and better communication with local markets, would also have positive impacts on profits. However, the costs of international innovation, including increase in coordination costs, possible rent-seeking behavior of subsidiaries, risk from uncertainty of the host country economy, and information leakage, would lead to negative impacts on profits. Summarizing the impacts and empirical studies on this topic, since it is hard to predict the effect of internationalization of innovation on profit through other channels, the final impacts of international innovation on profits is hard to predict. Due to the scope of this paper, we will only focus on the effect through the innovation channel (Hypothesis 1), and the final effect through all channels (Hypothesis 2), leaving the effects through other channels to further studies. Based on the observation of the popularity of international innovation and the close link of patents and profits in the pharmaceutical industry, we expect the positive impacts would overweight the negative impacts, therefore the final impacts of international innovation on profits would be positive.

Hypothesis 2: International innovation is expected to improve a firm's profitability.

Overall, the two hypotheses together test the effects of international innovation on firm performances, including both financial performance (Hypothesis 1), and innovation performance (Hypothesis 2). In other words, we examine the effects of international innovation on two aspects: profitability and innovation outputs.

1.4 Data

Our study is for the pharmaceutical and biotechnology industries, defined by North American Industry Classification System (NAICS): 325411 – Medicinal and Botanical Manufacturing; 325412 – Pharmaceutical Preparation Manufacturing; and 541711 – Research and Development in Biotechnology. For convenience, in this paper, we refer to firms in both industries as "pharmaceutical firms."

1.4.1 Sample

We include all top pharmaceutical firms in recent years. To get a listing of these firms, we referred to several online sources, including Current Partnering, PMLiVE, Contract Pharma and Wikipedia. Lists from these sources are all based on financial data after 2007 and include no more than 50 firms. We then combined them into a final list of big pharmaceutical firms in the U.S. and Europe. The top firms listed and used in this study include 172 firms worldwide. Since the study focuses on U.S and European firms and there are firms that we cannot find financial information, our final sample drops to 63 firms. The list can be found in Table A1 in the Appendix.

1.4.1.1 Patent data

Our patent data are from PubWEST, which includes patents from United State Patent and Trademark Office (USPTO), European Patent Office (EPO), and Japan Patent Office (JPO)1. We include only USPTO and EPO patents under corresponding pharmaceutical categories defined by IPC (International Patent Classification), which are A61K (Preparations for medical, dental, or toilet purposes) and C12N (Micro-organisms or enzymes; Compositions thereof; Propagating, preserving, or maintaining micro-organisms; Mutation or genetic engineering; Culture media).

To include all the patents for each firm, we made queries using both the names of the parent company and its subsidiaries. Public listed firms in U.S. are required to submit filings every year about their finance and operation. Therefore, 10-K is the most updated source for firm's subsidiaries. To simplify the procedure, we only use the most recent one, the 2012 10-K for U.S. firms.2 We referred to the 2012 10-K of most firms publicly traded in US for their subsidiaries information. Subsidiaries information for other firms is from Mergent Online. We also manually update the ownership of the patents for some firms for years after mergers and acquisitions.

1.4.1.2 Economic and Financial Data

[1] The JPO data provided by the PubWEST has only basic information with missing values for important fields, such as patent class, inventors, and the address of the inventors, so the JPO data is excluded from the sample. The other reason for the exclusion is that patent laws in U.S. and Europe are similar, while patent laws in Japan is much different. Therefore, every firm in our sample has patents from its home patent authority, and the patents are regulated by similar patent laws. These factors are very important for international patenting and international innovation.

[2] Due to the simplification, we are not able to have highly-accurate subsidiary information for each firm in each year. We assume that the change in subsidiaries are very small from year to year and firms will always keep patents under the name of the parent firm or existing subsidiaries unless they would like to sell their patents together with a subsidiary, which we do not capture in our data.

We collected the annual accounting data of publicly-traded pharmaceutical firms from the Compustat database[3]. Data on firms traded in USA and Canada are from Compustat North America, while data on other publicly traded firms are from Compustat Global. After matching firms on our list with those in the Compustat in the period from 1990 to 2010, we have a final sample of 63 firms.

1.4.1.3 Other Data Issues

Since our dataset comes from different data sources, we did more work to consistently combining data from different data sources together. Even though the two datasets from Compustat and PubWEST can be combined using corporate registration and identification information, inconsistences in year coverage exist between the two datasets. In other words, the starting year for a firm's patent data, the starting year for a firm's financial data, and the official or legal starting year for a firm might be different. After our manual treatment based on information from Bloomberg, Mergent Online, firm's own websites, and Compustat, a firm might have a different starting year from the starting year of the study period for one of the following two reasons: (1) the firm was formed by merging with another firm; (2) the firm was separated from another firm (spin-off). Likewise, a firm's ending year might be different from the ending year of the study period because it was later acquired by another firm.

[3] R&D data from Compustat include a lot missing and abnormal values, therefore, we instead collected R&D expenditure data from the annual financial reports provided by MergentOnline.

For patent data from PubWEST, some patents with US inventors have missing values in the inventor country field, but have values in the inventor state field. Therefore, the country information used in this study was in fact a combination of these two fields.

1.4.2 Variable definitions

1.4.2.1 Measures of firm performance

The previous literature uses different measures of financial performance. For example, Fors (1997) used parent firm growth, while Todo and Shimizutani (2008) used parent firm productivity. In this paper, we regard the financial performance measure as a final measure of the effect of international innovation. Therefore, we use the profitability of the whole company. Three measures of profitability are commonly used in the literature: (1) Return on Assets (ROA), which is net income divided by total assets; (2) EBIT (Earnings before Interests and Taxes) divided by total assets to measure firms' profitability. This is a commonly used measure of profitability (e.g. Dewenter and Malatesta, 2001). Unlike net profit, EBIT exclude all possible biases caused by firms' financial strategies; (3) net profit rate, which is net income divided by total sales. The first two measures measure how much profit a firm can generate from its current assets. The last measure measures how much affirm can keep as profit from its sales income. In this paper, we investigate the impacts of the international innovation on firms' profits. We expect firms would have improvements on its research capability or R&D productivity through internationalization of innovation, therefore, the number of inventions should also increase. Inventions and other knowledge on production are important components of a firm's intangible assets, therefore, important components of the total assets. In addition, the

correlation of the first two measures and the indicators of internationalization of innovation are higher than the correlation between the last measure and the indicators. Hence, the profitability measures based on total assets (first two measures) are more appropriate to use in the study. Since the estimation results of the first two measures are very close to each other, we only show the estimation results using the first measure. The summary statistics and estimation results of the other two measure can be found in the Appendix.

Patents are awards to firms' research activities and are often linked to new technologies introduced the market. Patents are considered as the outputs of a firm's innovation efforts (Pakes, 1985, Griliches, 1980) in this paper. Pharmaceutical industry, overall, has a very high patenting rate and patents are critical to a firm's success (Scherer at al., 1959; Mansfield, 1986; Levin et al., 1987; Coad and Rao, 2008; Helmers and Roger, 2011; etc.). According to a survey by researchers at Carnegie-Mellon University in 1994 (Cohen et al., 2000), pharmaceutical firms reported that 78% of their business units filed for patents. In the literature, both patent applications and patent grants are used to count patent numbers. Due to the patenting process, there is a considerable time lag from filing to granting. Therefore, the patent application4 is a better measure of a firm's innovation outcome.

1.4.2.2 Measures of internationalization of innovation

Researchers have used different methods to measure the internationalization of innovation. These include survey-based measures (Panner-Hahn and Shaver, 2005), R&D

[4] Generally, not all patent applications will be granted. One of the common reasons for the failure is that the patent authority does not think the invention is not innovative enough, so the patents grant is believed to be a better measure of innovation. To accommodate both the quality of the invention and the timing of the process, we use successful patent applications in our dataset.

expenditure-based measures (Belderbos et al., 2007), and patent-based measures (Quintás et al., 2008). In this paper, we use patent-based measures.

We use patent inventor address information to find evidence of international innovation. The output of international innovation would naturally be patents with inventors from foreign countries. Based on different hypotheses, researchers proposed different approaches to use the address of inventors to decide whether a patent is the output of international innovation, including first-inventor counting (i.e. assign a patent to the country where the first inventor comes from), multiple-counting (i.e. every country where the inventors come from gets one patent count), fractional-counting (i.e. every country where the inventors come from gets a fraction of one patent count), majority-counting (i.e. assigning a patent to the country where most of its inventors come). Therefore, the first and last approach would cause a patent to be assigned only to one country, while the second and third approach might cause a patent to be assigned to more than one country. According to OECD (2004), the first-inventor counting is the most commonly used approach, which is supported by two hypotheses: first, the first inventor is generally considered as the most important contributor to a patent; second, the country from which the first inventor of a patent comes generally reveals the origins of the invention (Cantwell and Kosmopoulou, 2001; Trajtenberg, 2001). Bergek and Bruzelius (2010) compared different approaches mentioned above in a case study of a Sweden pharmaceutical company, ABB. They found that, using information from interviews with patent inventors as the base line, none of the approaches generated substantially differences in results, although general differences did exist among different approaches. Combining these reasons, our use of address of the first

inventor seems well-grounded in the literature. Below we describe the alternative measures.

Internationalization Indicator 1

Indicator 1 equals the percentage of patents granted by foreign patent authorities out of the total number of patents of the firm from both EPO and USPTO. For example, if a firm in U.S. have 100 successful applications from EPO, and 200 from USPTO, then Indicator 1 = 100/ (100+200) =33%.

International patenting is a common practice that a firm have the same invention pated in both home and foreign country (countries). Motivations for international patenting mainly include: more protection of important technology, or exclusive selling right in foreign market. Since the invention protected by international patenting can be produced at either home country or foreign country, firms involve in international patenting might not necessarily involves in international innovation. However, these firms at least have more consideration on international production, operation, or marketing, therefore, they are more likely to involve in international innovation now and in the future. However, since Indicator 1 use the total number of patents granted by both home and foreign patent authority, it is likely to include double-counting of the same invention. Therefore, Indicator 1 is just a gross indicator of international innovation, which serves as the beginning point of our measurement of international innovation.

Internationalization Indicator 2

Indicator 2 equals the percentage of patents with foreign inventors out of all the patents granted by home patent authorities. That is, for a firm from Country i, if m is the number of patents with foreign inventors, then Indicator 2 $=\frac{m}{n_i}$.

In most cases, international innovation is conducted by scientists in foreign countries who later became the inventors of patents. In other words, innovational innovation often results in patents with foreign inventors. Due to the importance of home country market and safety of technology, firms would have all their inventions patented in their home countries in most cases. Therefore, Indicator 2 should represent the percentage of international innovation out of a firm's total innovation.

In addition, since the total used in this measurement is the patents granted by only home patent authority there is no double-counting issue here. However, in some cases, firms might consider an invention in the foreign county is not important for the home market and have no safety issue for the invention to be only protected in the foreign country. Then they would not patent the invention created in a foreign country through the home patent authority., For this case, Indicator 2 would miss the international innovation for the firm and has a value less than the true percentage of the firm's international innovation. We expect this doesn't apply to many firms in most case, so although Indicator 2 might not be an accurate measure, it is at least lower-bound of the true international innovation.

Internationalization Indicator 3

Indicator 3 counts the number of years since a firm's first patent with first inventor with addresses outside of the home country. This measure is built according to Quintás et al. (2008), in which the measure is named "international technological experience".

As mentioned earlier, international innovation is associated with many different types of benefits and costs. Therefore, firms need to develop their own strategy to maximize the benefits and to minimize costs. Firms, which start international innovation early, should have more experiences to develop and employ their strategies. If we use patents with the first inventor with addresses out of the firm's home country as the evidence of international innovation, the first patent of that kind should mark the beginning of the firm's international innovation. 5

It is possible for a firm to have a patent with a foreign inventor 10 years ago, but still involved little international innovation now. We argue that this type of firms should still have more knowledge on internationalization of innovation than firms without any patents with foreign inventors yet. What's more, we leave the measure of the volume as the focus of the first two indicators.

Internationalization Indicator 4

[5] Since our data are collected for patents applied from 1990 to 2010, the maximum for this indicator would be 21 for all firms in all years. However, if a firm participated in international innovation earlier than 1990, this indicator will still give a value of 21. Thus, this indicator has a truncation problem. However, after digging into the data, we find this would not cause a lot harm to our analysis, because the maximum for Indicator 3 is 19. The mean of Indicator 3 at 2010 is 3.4. This means that the case that a firm involved in international innovation earlier than 1990 rarely happens. Therefore, the truncation problem of the data would not seriously affect the validity of our analysis.

Indicator 4 counts the number of countries the first inventors come from, using all the patents applications filed to the home patent authorities in a certain year. This indicator is built based on the measure named "geographical amplitude" in Quintás et al. (2008).

Every inventor with a foreign address brings the firm with new ideas, technologies, or market information to the firm's knowledge pool. More countries the firm taps into, more foreign inventors would join the firm to produce knowledge, more foreign knowledge the firm could learn, therefore, more patents would be applied by inventors outside of the home country.

It is possible that a firm might have 10 foreign inventors in total, but all of them came from the same foreign country, and another firm might also have 10 foreign inventors in total, but each of them comes from a different country. It is hard to say which of the two is more involved in the internationalization of innovation. But Indicator 4 shows us the Second firm has a broader view in the international innovation. However, same as Indicator 3, Indicator 4 only measures the width of the knowledge pool, or the geographical amplitude, and leaves the volume of the international innovation to be measure by the first two indicators.

1.4.2.3 More Discussion on the Internationalization Indicators

To summarize, Indicator 1 measures international patenting; Indicator 2 measure the "volume" of the international innovation; Indicator 3 measures the "depth" of a firm's international knowledge pool, or global technological experience; and Indicator 4 measures the "width" of the firm's international knowledge pool. Each indicator measures from different perspectives, and has its limitation. Therefore, the four indicators are not

replacements for each other, but complements. Using all of them, we can measure different dimensions and have a better picture of the international innovation. To make the four indicators comparable in magnitude, we standardized the four indicators with zero means and unit variance.

Table 1 - Indicators

Variable	Obs	Mean	Std. Dev.	Min	Max
ind1	1,025	3.43E-09	1	-1.29558	2.263565
ind2	1,025	7.83E-09	1	-0.66131	2.819209
ind3	1,025	1.54E-08	1	-2.02748	1.406342
ind4	1,025	-6.83E-10	1	-0.99762	4.572498

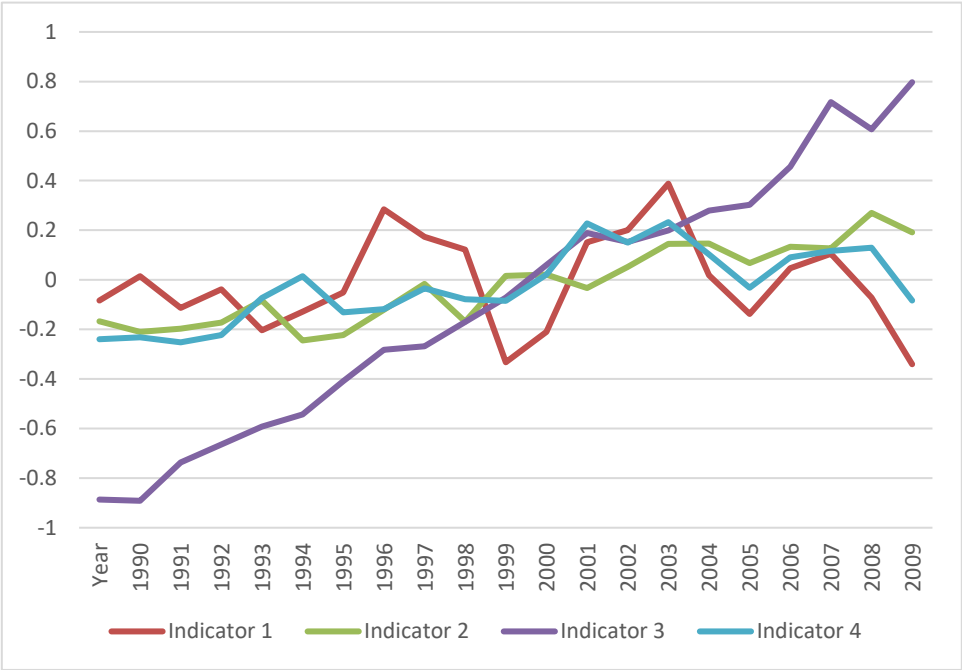


Figure 1 - Four indicators of internationalization of innovation

The summary statistics is shown in Table 1. The correlation between indicators range from 0.1124 to 0.395, Figure 1 shows the trends for the four indicators. All the indicators have an increasing trend, although the rate of increase differs, with higher rate of increase for IND4 than other three. Combining the indicators together, we can have more information of the firms. Indicator 3 can help us find starter and existing firms involved in the internationalization of innovation. Indicator 1 or Indicator 3 can give us how much international innovation were created by the firm. Therefore, we can have the firms in the sample divided into 4 types.

Table 2 - Firm Types by Indicators

Firm type	Indicators	Percentage
Slow starter	Low Indicator 3, low Indicator 1 and 2	20.8%
Quick starter	Low Indicator 3, high Indicator 1 and 2	31.9%
Winner	High Indicator 3, high Indicator 1 and 2	18.15%
Loser	High Indicator 3, low Indicator 1 and 2	7.32%

We find that 20.8% of the sample are slow starters, 31.9% of the sample are quick starters, and 18.15% are winners. The high percentage of quick starters, and 18.15% are winners. The high percentage of quick starters and lower percentage of winners can all be partly explained by the property of the sample. The sample is all top pharmaceutical firms. They should have better size and research capability to begin international innovation. As the time went on, the percentage of international innovation would be driven down by the increase in the total innovation output. We use this classification to add dummies of firms type into the estimation. The results are discussed in later parts.

1.4.3 Preliminary Data Analysis

In this section, we conduct a preliminary analysis of our data to highlight various characteristics related to the internationalization of innovation.

Main variables used in estimation are listed in Table 2 with their labels and brief definition. Table 3 reports descriptive statistics for main variables in the study. Our sample includes 63 firms in the pharmaceutical industry from the U.S. and Europe over the period 1990-2010.

Table 3 - Variable List

Variable Name	Name	Definition
PAT	Patent application counts	Counts of patent applications filed by a firm in a certain year
pstock	Patent stock	The sum of patent application counts in the last three years as the measure for research capability
rd_real	R&D in real values	R&D spending adjusted by GDP deflator for OECD countries (base year 2010)
rd_intensity	R&D intensity	R&D spending divided by sales
sale_real	Sales in real values	Sales adjusted by GDP deflator for OECD countries (base year 2010)
Ind1	Indicator 1	International patenting
Ind2	Indicator 2	Volume
Ind3	Indicator 3	Depth of the knowledge pool
Ind4	Indicator 4	Width of the knowledge pool
Profit1	Profit measure 1	ROA
Profit2	Profit measure 2	EBIT/total asset
Profit3	Profit measure 3	Net income/sales
EMP	Employee numbers	Number of Employees in thousands
MA	M&A dummy	MA=1 if the firm has M&A in the year

Note: Lagged variables are not listed here. Lagged variables are simply the previous values of the variables listed here and are named by adding letter "L." in front of the original variables. For example, L.ind1 is the lagged value for ind1, i.e. the previous value of indicator 1. If it is the two-year lagged, then the variable would begin with "L2.".

Table 4 - Descriptive Statistics

Variable	Mean	Std. Dev.
pat	**72.07**	**133.06**
pstock	**220.74**	**394.95**
rd_real	**994.79**	**1,793.01**
rd_intensity	**4.58**	**31.69**
ind1	**0.00**	**1.00**
ind2	**0.00**	**1.00**
ind3	**0.00**	**1.00**
ind4	**0.00**	**1.00**
profit1	**-0.11**	**0.38**
profit2	**-0.07**	**0.38**
profit3	**-5.45**	**41.67**
ebit	**1,627.13**	**3,292.19**
ni	**1,058.65**	**2,407.19**
sale_real	**4,291.02**	**7,442.22**
ma	**0.76**	**2.13**
emp	**21.64**	**34.32**

In Figure 2, we compare the trends of patent applications by the firms in our sample to EPO and USPTO. Despite the changes in the number of patent applications to EPO in recent years, the two patent authorities are generally comparable in terms of patent applications volume. Therefore, although we only use U.S. and European patents of U.S. and European firms, the dataset is representative of the world patents and firms.

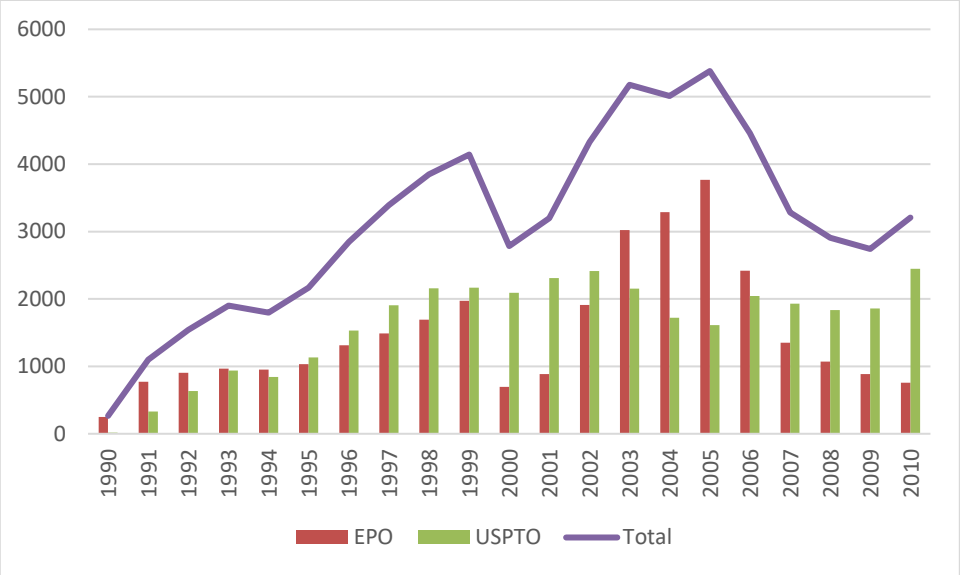
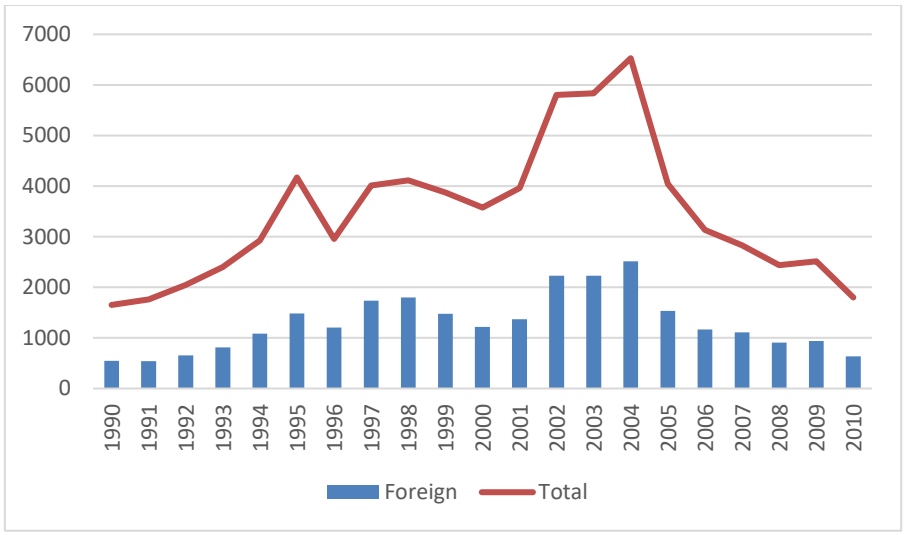
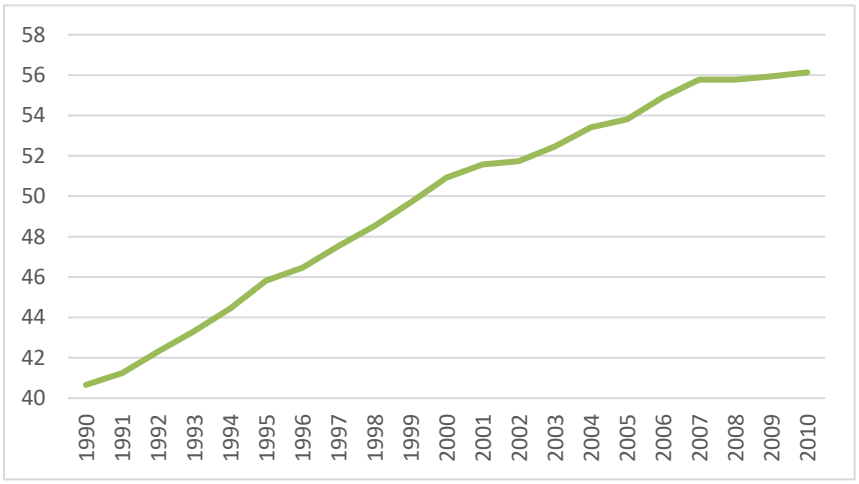


Figure 2 - Trend of patent application numbers: by patent authorities

In this paper, we use the address of the first inventor to provide evidence for the internationalization of innovation. If the inventor has a foreign address, it is very likely that the inventor lived or worked in the foreign country when the invention was completed, therefore the patent is very likely to be the outcome of R&D using foreign resources. Although due to the data limitations we only have the address information for the first inventor, we discuss in next section that this is a most commonly used measure of international innovation. Using this measure, Figures 3 to 5 display the general trends in internationalization of innovation over our sample period.

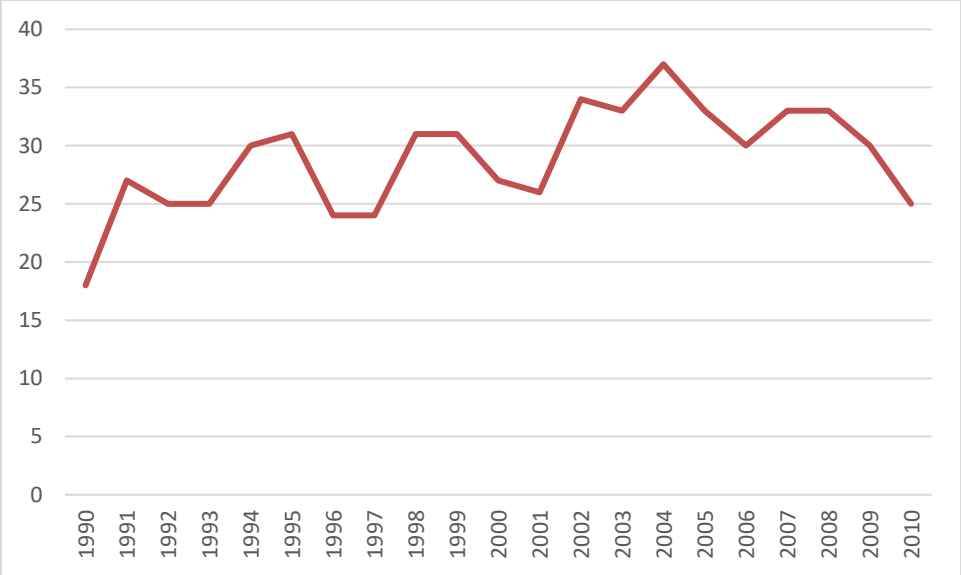


a. Trend of international innovation: total patents

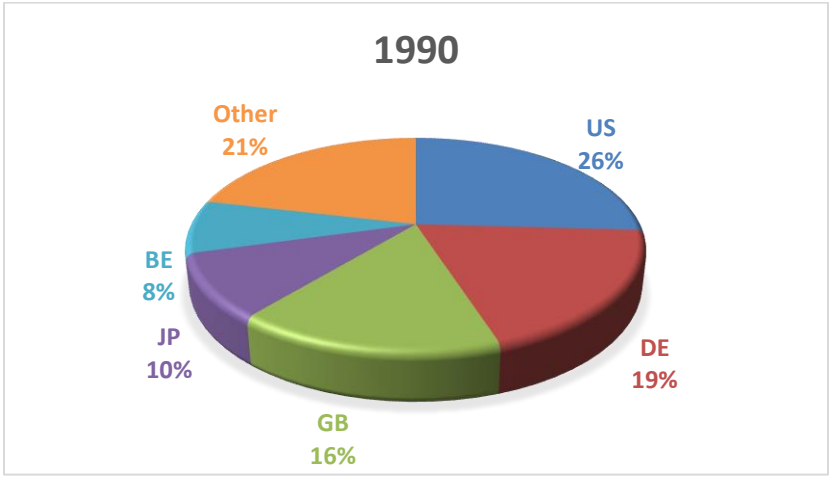


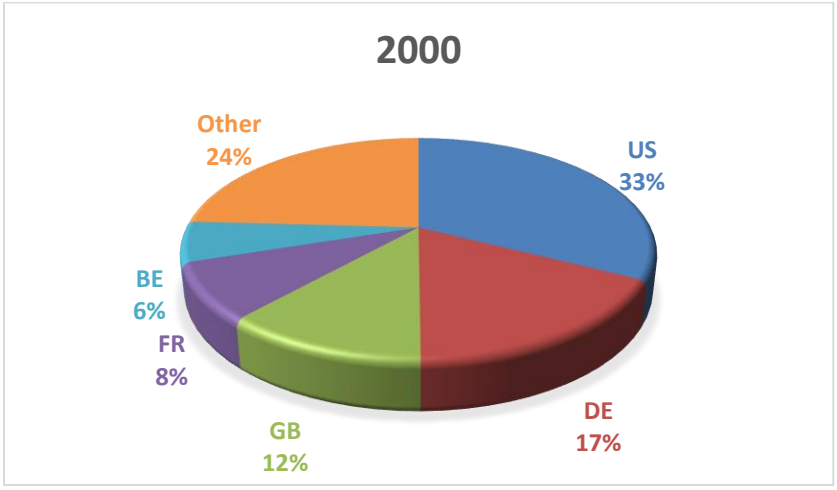
b. Trend of KOF indicator

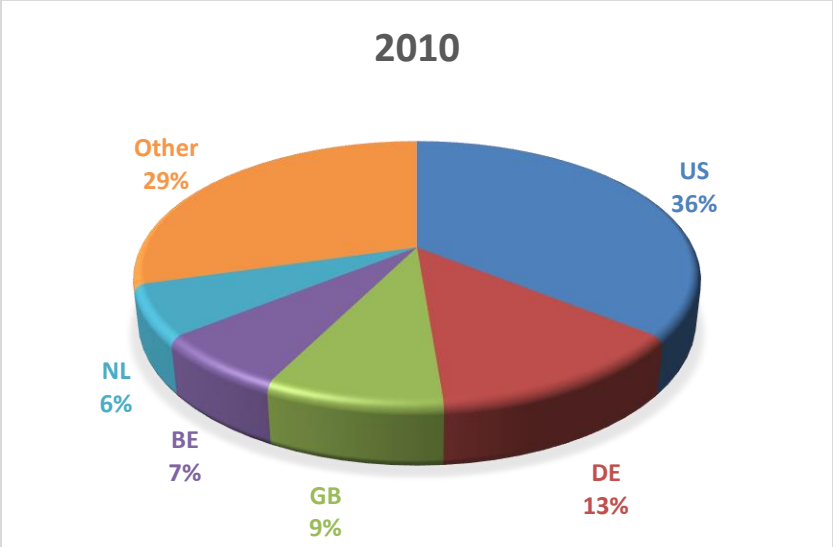
Figure 3 - Trend of internationalization of innovation



a. Trend of countries involved in international innovation







b. Top five host countries, 1990, 2000, 2010

Figure 4 - Countries involved in internationalization of innovation

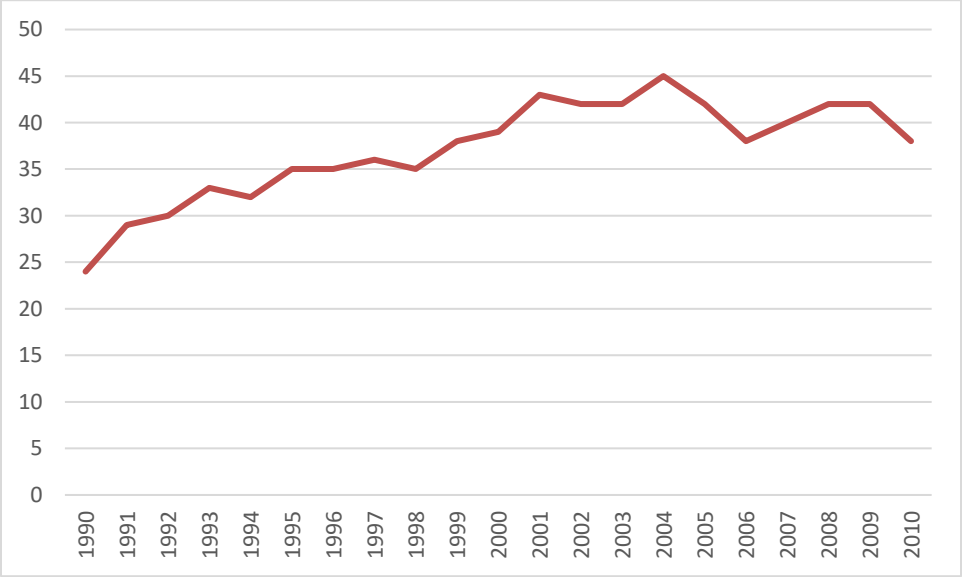


Figure 5 - Trend of firms involved in international innovation

As shown in Figure 3a, from 1990 to 2010, the number of patents of international innovation has been increasing with only small drops recently. Since internationalization of innovation is part of globalization, it might follow the same trend as globalization. Here

we choose the KOF Indicator of Globalization to find the trend of globalization. Figure 3b shows us globalization indeed had a similar path as international innovation, particularly for the decrease in recent years. From Figure 4a and Figure 5, we can see that both the number of countries and the number of firms involved in international R&D are in general increasing during the sample period with fluctuations. Both numbers were nearly steady in recent years, which might indicate a slowdown of international innovation. Figure 4b shows us the composition of the international innovation. The US, Germany, and Great Britain remain in the top three without change in the ranking even. They account for around 60% of the total international innovation. Even though the total amount the top three accounts do not change much, the amount by US has been increasing, from 26% to 36%. Belgian always ranks 4th or 5th. Besides the top five countries, the amounts by other countries has been increasing slow from 21% to 29%. To summarize, these charts is consistent with the previous chars in that more and more countries are involved in the internationalization of innovation. However, the center place of US as the country involved most has also been enhancing through the sample period.

Through the trend of patenting of all the firms in the sample, we have a general understanding of the international innovation over our sample period. The increasing trend of international innovation provide general support for the effects of international innovation on firm performance.

1.5 Estimation Strategies

We employ different methods for estimating the effects of uncertainty: (1) negative binomial and Poisson estimator for innovation performance, (2) dynamic panel model for financial performance.

The patent production function is widely used in patenting studies (e.g. Hall and Ziedonis, 2001; Hu and Jefferson, 2009). We specify our augmented patent production function as:

$$E(PAT) = \exp\left(\boldsymbol{V'\beta_V} + \boldsymbol{IND'\beta_I}\right) \quad (1)$$

where PAT is the count of patent applications[6], the vector V stands for traditional explanatory variables in the patent production function, including R&D expenditures, firm size, research capability and other variables. IN is the international innovation.

Taking logarithm for both sides and specifying our estimation function as:

$$ln\left(PAT_{i,t}\right) = \beta_0 + \beta_1 IND_{i,t-1} + \beta_2\, ln\left(RD_{i,t-1}\right) + \beta_3\, ln\left(pstock_{i,t-1}\right) + \beta_4 Sales_{i,t-1} + MA_{t-1} + \gamma_i + \delta_t + u_{i,t} \quad (2)$$

where IND is still the indicator of international innovation, RD is R&D intensity, pstock is the patent stock, and u is the error term. 7

Since the dependent variable is patent counts, we employ Poisson and Negative binomial regression models, which are commonly used in studies of patent output (e.g.

[6] Since PAT = 0 occurs, we have all the PAT added by 1, so PAT starts from 1, even though the firm did not file for a patent in that year. This would not affect the results much, because firms in our sample are all big firms in the industry with high volume of patent applications. The mean of PAT in our dataset is about 70, and it has a variance of 132.

[7] Since zero values were found for some firms at some years, we added 1 to PAT, therefore, the patent number start from 1, and are suitable for logarithm.

Henderson and Cockburn, 1996; Hall and Ziedonis, 2001; Penner-Hahn and Shaver, 2005; Hu and Jefferson, 2009). For the fixed effect Negative Binomial regression models, there is a potential "incidental parameters problem". We have noticed several options to deal with this type of problem. We will address this potential bias later on.

Our interested independent variables are the indicator variable. As mentioned earlier, the indicators on the right-hand side is patent-based measures. Except for IND1 in which we use PAT as its denominator, other indicators are correlated with PAT, but do not use PAT as a component. The correlation between PAT and IND1 to IND3 is not high, ranging from 0.06 to 0.16. The correlation with IND4 is exceptionally high, 0.78, but IND4 counts the number of countries, which are not linearly correlated with PAT. What's more, since the indicators are included separately into the model, one at a time. Hence, problems with any indicator would not affect the results of other indicators. Therefore, including indicators as explanatory variables should not create severe problems in our models. We include R&D expenditure as the input for innovation. R&D expenditure is a long-term investment, which takes time to have impacts (Barker and Mueller, 2002). However, it is generally difficult to identify the lag structure of the impacts. Moreover, the lag structure is likely to be different among firms and projects. As discussed in Hall and Ziedonis (1995), due to "the high within-firm correlation of R&D spending over time", the estimation results among R&D variables with different lag periods are "roughly the same". So here we use one-year lagged R&D to be consist with other variables in the model. We measure research capability as firms' patent stock for the previous three years. R&D spending is scaled by sales, which is often called R&D intensity.

We adjusted firms' nominal sales to base year 1990, using Producer Price Index from U.S. Bureau of Labor Statistics for the pharmaceutical industry. We use sales here as a control variable for firm size, so we use contemporaneous value of sales. Following Penner-Hahn and Shaver (2005), we use the sum of patent counts in the last three years as a measure of firms' underlying research capabilities. We use last three-year period is to capture recent research skill while reducing the effects of random, extreme event in certain years.8

As a general measure of the outcome of firms' operations, firm performance could be affected by all aspects, including firms' resource, strategy, management, and environment. Using a model which cannot capture all the important factors that affects firm performance could generate many bias and problems to the estimation. To deal with this problem, we employ the dynamic panel model using all the past information of firm performance as the instrument.

For testing Hypothesis 2:

$$Profit_{i,t} = Profit_{i,t-1} + IND_{i,t-1} + MA_{i,t-1} + \alpha_i + \delta_t + \epsilon_{i,t} \qquad (3)$$

where profit is the measure of profitability, IND is the indicator for international innovation, and MA is the dummy variable for M&A.

The lagged dependent variable, also acts as an important control variable here. It controls at least two types of factors: (1) possible persistence in the intertemporal path of profit; (2) omitted firm-specific time-varying factors that might affect the intertemporal

[8] Penner-Hahn and Shaver (2005) tested that their results were not sensitive to the length of period.

path of profit. Therefore, our models are dynamic panel models. Since the lagged dependent variable is necessarily correlated with the idiosyncratic error, strict erogeneity in the regression is violated. Commonly used static panel data techniques such as fixed effects estimators would be inconsistent. To deal with this problem, we used the most popular Arellano-Bond estimator for the dynamic panel model, which is a generalized method of moments (GMM) estimator.

M&A could have a significant influence on firms' financial and economic performance, knowledge stock and research capability. For example, a firm might acquire another firm mainly for its technology. M&A also bring changes to the ownership of patents. Therefore, we have a dummy for M&A if it happened in the previous year, given that the effects might occur with some delay. Although the firms in our sample are all top firms, in the pharmaceutical industry, the size of the firms varies significantly. Therefore, we also include the number of employees as the measure for firm size.

We use clustering errors for all models in the paper. For panel data, where observations can be grouped into clusters, model errors might be uncorrelated across cluster but correlated within cluster, therefore, controlling for within-cluster error correlation is needed. Failing to control for within-cluster error correlation can lead to smaller standard errors, narrow confidence intervals, large t-statistics, and low p-values (Cameron and Miller, 2015). Therefore, clustering errors is applied to every model and estimation where feasible.

For linear regression model, the traditional way to control for clustered errors is to estimate a model specified for the within-cluster error correlation, and then estimate the

original model by feasible generalized least squares (FGLS) rather than ordinary least squares (OLS). However, the model only generates valid statistical inference, and more efficient estimates under the strong assumption that the model for within-cluster error correlation is correctly specified. (Cameron and Miller, 2015).

A more recent method to control for clustered errors is to estimate the regression model limited or no control for within-cluster error correlation, and then obtain "cluster-robust" standard errors. For the fixed-effects estimator in linear panel models, the cluster-robust standard errors are provided by Arellano (1987). The method was incorporated into Stata by Rogers (1993). When using the Arellano-Bond estimator, it is required to test whether the remaining error U_{it} it is serially correlated. Generally, including fixed-effects at cluster level does not control for all the within-cluster correlation of the errors. It is standard to test whether it is sufficient to estimate without cluster-specific fixed-effects. We will discuss these tests in the estimation part. Even though pharmaceutical firms in our sample are all top firms in the same industry, they still vary greatly in size, profitability, and business lines. Therefore, we do cluster by firms.

1.6 Estimation Results

1.6.1 International innovation and innovation performance

Due to the nature of the dependent variable, we estimate the models using Poisson and Negative Binomial regression method for panel data. In Table 4, we list both fixed and random effect estimation results for the two methods. The four indicators are shown to have different impacts on patent production. IND1 has coefficients all negative, and none of them are significant. Therefore, it is hard to conclude that IND1 has impacts on patent

production. IND2 has two coefficients positive and two negative, with only one of the positive significant. Therefore, we can only conclude that IND2 might have positive impact on patent production. The coefficients of IND3 have two positive and two negative coefficients with the positive ones significant, indicating that experience in international innovation has some positive impacts on innovation. All the coefficients for IND4 is significant and positive so width of the knowledge pool matter the most for innovation. Combining the impact of the four indicators, we conclude that international innovation would improve firms' innovation performance. Working with more countries and widening the knowledge pool of international innovation is proved to be more important that other aspects.

Table 5 - Estimation Results for Model 1

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
VARIABLES	pat	pat	pat	pat	pat	pat	pat	pat
	Poisson RE	Poisson FE	Negative Binomial RE	Negative Binomial FE	Poisson RE	Poisson FE	Negative Binomial RE	Negative Binomial FE
pstock	0.000749***	0.000749***	0.000732***	0.000730***	0.000748***	0.000747***	0.000738***	0.000733***
	(7.05e-05)	(7.04e-05)	(0.000171)	(0.000195)	(7.28e-05)	(7.26e-05)	(0.000158)	(0.000144)
L.rd_intensity	-0.00268	-0.00262	-0.00176	-0.00163	-0.00268	-0.00262	-0.00175	-0.00163
	(0.00242)	(0.00237)	(0.00356)	(0.00514)	(0.00242)	(0.00237)	(0.00267)	(0.00329)
L.ind1	0.00487	0.00500	-0.00538	-0.0103				
	(0.0362)	(0.0362)	(0.0314)	(0.0289)				
L.ind2					-0.0169	-0.0172	0.0729*	0.0649
					(0.0688)	(0.0691)	(0.0407)	(0.0490)
L.ind3								
L.ind4								
L.sale_real	-3.66e-05***	-3.69e-05***	-2.22e-05*	-2.48e-05**	-3.63e-05***	-3.65e-05***	-2.36e-05*	-2.60e-05**
	(9.64e-06)	(9.60e-06)	(1.19e-05)	(9.80e-06)	(9.59e-06)	(9.55e-06)	(1.36e-05)	(1.11e-05)
L.ma	0.00183	0.00175	0.0203**	0.0195**	0.00212	0.00204	0.0189	0.0183**
	(0.0121)	(0.0122)	(0.00897)	(0.00851)	(0.0126)	(0.0127)	(0.0119)	(0.00855)
Constant			1.394***	1.415***			1.403***	1.425***
			(0.164)	(0.151)			(0.132)	(0.128)
Observations	834	833	834	833	834	833	834	833
Num of firms	61	60	61	60	61	60	61	60
Log-likelihood	-7599	-7141	-3447	-2996	-7598	-7140	-3444	-2994
Chi2	705.3	144.9	75.92	36.11	717.6	135	73.15	63.29

Table 6 (continued)

	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)
VARIABLES	pat	pat	pat	pat	pat	pat	pat	pat
	Poisson RE	Poisson FE	Negative Binomial RE	Negative Binomial FE	Poisson RE	Poisson FE	Negative Binomial RE	Negative Binomial FE
pstock	0.000750***	0.000750***	0.000732***	0.000726***	0.000654***	0.000655***	0.000541***	0.000552***
	(7.09e-05)	(7.07e-05)	(0.000164)	(0.000125)	(8.25e-05)	(8.22e-05)	(0.000132)	(0.000162)
L.rd_intensity	-0.00272	-0.00266	-0.00159	-0.00149	-0.00261	-0.00254	-0.00157	-0.00146
	(0.00246)	(0.00241)	(0.00272)	(0.00267)	(0.00232)	(0.00228)	(0.00379)	(0.00305)
L.ind1								
L.ind2								
L.ind3	-0.0151	-0.0146	0.173***	0.160**				
	(0.102)	(0.103)	(0.0645)	(0.0762)				
L.ind4					0.147***	0.145***	0.275***	0.253***
					(0.0464)	(0.0460)	(0.0420)	(0.0466)
L.sale_real	-3.58e-05***	-3.60e-05***	-3.10e-05***	-3.33e-05***	-3.76e-05***	-3.78e-05***	-3.02e-05**	-3.21e-05***
	(9.16e-06)	(9.17e-06)	(1.12e-05)	(1.27e-05)	(9.10e-06)	(9.05e-06)	(1.18e-05)	(1.09e-05)
L.ma	0.00241	0.00231	0.0128	0.0124	-0.00188	-0.00193	0.00550	0.00586
	(0.0130)	(0.0131)	(0.0120)	(0.00965)	(0.0131)	(0.0131)	(0.0129)	(0.0122)
Constant			1.446***	1.471***			1.496***	1.515***
			(0.156)	(0.122)			(0.115)	(0.138)
Observations	834	833	834	833	834	833	834	833
Number of firms	61	60	61	60	61	60	61	60
Log-likelihood	-7598	-7140	-3434	-2985	-7402	-6948	-3418	-2972
Chi2	764	137.6	65.56	63.33	893	182.3	165.1	100

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Notes: The models are estimated using the Arellano-Bond estimator by Arellano and Bond (1991) and implemented by STATA 13 by Roodmand (2009). Robust cluster errors (clustered by firm) are reported in braces. Robust clustered standard errors are implemented by STATA 13 Roger (1994). Year dummies were used in each model. Instrument sets of lagged depend variable (GMM style) and all other right-hand-side variables (IV style). The

following tests are applied: 1. The Hansen test as a test of erogeneity and validity of instrument subsets; (Since we are using robust clustered standard errors, Sargan test is inappropriate.) 2. AR(2) test as a test for second-order serial correlation, required by suing the Arellano-Bond estimator; 3. The Wald test with the null hypothesis that all the coefficients except the constant are zero. All tests are reported by their p-values for convenience.

1.6.2 International innovation and financial performance

Estimation results for financial performance are presented in Table 5. The models are estimated using the Arellano-Bond Estimator for dynamic panel data models. The profit measure has very significant coefficients across all models, so the profit consistence is statistically confirmed. Indicator 2, 3 and 4 have significant positive effects on profits, with IND4 having magnitude and IND2 having the highest significance, while Indicator 1 don't have significant impacts. Combining the impacts of the four indicators, we can easily conclude that international innovation would increase profit. All the models for the financial performance well pass the tests of overidentification constraints and serial correlation. This is generally consistent with the finding of the impacts of international innovation on innovation performance. Working with more countries and experience create more profits for the firms, while volume of the international innovation does not seem to be as important as the other two. This confirms our argument about the relationship between the impact son two types of performance. That is, the main channel of impact of internationalization of innovation of financial performance is through increase in research capability and productivity.

Table 7 - Estimation Results for Model 2

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)
VARIABLES	profit1	profit1	profit1	profit1	profit2	profit2	profit2	profit2	profit3	profit3	profit3	profit3
L.profit1	0.426***	0.415***	0.392***	0.397***								
	(0.0916)	(0.0933)	(0.115)	(0.0996)								
L.profit2					0.512***	0.513***	0.477***	0.474***				
					(0.125)	(0.130)	(0.153)	(0.145)				
L.profit3									0.270**	0.269**	0.273**	0.270**
									(0.130)	(0.130)	(0.130)	(0.131)
L.ind1	0.0322				0.0415*				2.316			
	(0.0242)				(0.0217)				(1.859)			
L.ind2		0.0671**				0.0365				0.789		
		(0.0319)				(0.0391)				(1.529)		
L.ind3			0.0940**				0.103**				-1.177	
			(0.0434)				(0.0442)				(2.025)	
L.ind4				0.174**				0.197				-0.910
				(0.0860)				(0.130)				(3.229)
L.ma	0.00611	0.00540	0.00500	0.000273	0.00220	0.00223	0.000151	-0.00469	-0.0546	-0.0329	0.00652	0.0127
	(0.00374)	(0.00395)	(0.00348)	(0.00456)	(0.00269)	(0.00273)	(0.00228)	(0.00565)	(0.0969)	(0.0915)	(0.0683)	(0.130)
L.emp	0.00173***	0.00164***	0.00138***	-0.00167	0.00156***	0.00157***	0.00122**	-0.00222	0.0331**	0.0382***	0.0479**	0.0598
	(0.000493)	(0.000468)	(0.000371)	(0.00158)	(0.000605)	(0.000563)	(0.000505)	(0.00219)	(0.0130)	(0.0130)	(0.0227)	(0.0755)
Constant	-0.0209	-0.0103	0.0623*	0.0769	0.00146	0.00338	0.0919**	0.111**	-5.855	-6.164	-7.573	-6.926
	(0.0518)	(0.0508)	(0.0366)	(0.0468)	(0.0603)	(0.0579)	(0.0407)	(0.0454)	(5.198)	(5.139)	(6.695)	(6.219)
Observations	906	906	906	906	908	908	908	908	873	873	873	873
Number of firms	61	61	61	61	61	61	61	61	61	61	61	61
Wald test (p-value)	0	0	0	0	0	0	0	0	0	0	0	0
AR(2) (p-value)	0.374	0.329	0.288	0.439	0.721	0.618	0.577	0.775	0.938	0.794	0.670	0.670
Hansen test (p-value)	1	1	1	1	1	1	1	1	1	1	1	1

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Note: For each indicator, the model is estimated using Poisson estimator Random Effect (RE) and Fix Effect (FE), and Negative Binomial Estimator Random Effect (RE) and Fixed Effect (FE). Robust cluster errors are reported in braces except for Poisson FE with robust standard errors. All constants are omitted. Log-likelihood test with null hypothesis that some arbitrary group of k coefficients in the model is equal to zero, are applied. The Wald test with null hypothesis that all the coefficients except constant are zeros, are applied.

1.6.3 Robustness Check

We also examine the impacts of internationalization of innovation through some variations of the two main models as robustness check. First, as mentioned earlier, we are able to define different types of firms based on the values of the indicators of international innovation. In one of the variation of Model 1, we include dummy variables for firms identified as “winner”, “slow starter”, and “quick start”. Although none of coefficients for the dummy variables are found to be positive the significance of the coefficients for indicators improved a bit. The estimation results can be found in the Appendix.

Second, since there are several powerhouse countries in the terms of the international innovation and biotechnology development, the country where the firm comes form might also have significant impacts on the financial and innovation performance. Therefore, we have dummy variables added to the estimation to identify the country when the firms come from. However, the coefficients on these variables were not found to be significant, nor did the inclusion of these variables have benefits on other parts of the models. The reasons behind this might be that the firms in the sample are mainly form these “powerhouse” countries and all of them are large multi-national firms, which have several competitive R&D centers indifferent locations, as discussed in Gassman and Van Zediwitz (1999). The estimation results are not included in the paper.

Thirdly, although all firms are from the pharmaceutical industry, there are commonly two types of firms in the industry: (1) biotechnology firms focusing on research and development, and (2) life sciences firms focusing on additional development and the marketing of resulting products, as discussed in many studies (e.g. Reuer et al, 2002;

Robinson and Stuart, 2007; Sturt et al, 2007). We obtain additional information from Bloomberg on the business lines of the firms in our sample None of them are identified as primary involved in the biotechnology, but some of the them partly involved in biotechnology. Therefore, this should not matter much for our sample. We added a dummy variable for those biotechnology firms. As expected, it didn't have significant coefficients, nor did it help with investigating other impact. The estimation results are not included in the paper.

Finally, since our indicators measure different aspects of the internationalization of innovation and the correlation between them is not very high due to the difference in the definition. We also tried a variation of the estimation by including all the indicators in one model. However, the results are very clear. Even though the indicators are different by definition and correlation, it still measures the same phenomenon. Almost all the indicators are insignificant. The significance of other variables is also affected. The estimation results are included in the Appendix.

1.7 Conclusions

Using patents data for relatively large multinational pharmaceutical firms, we build four indicators to measure the internationalization of innovation. Combining the patents data with the financial data of the firms enables us to estimate the effects of international innovation on firms' financial and innovation performance. We find evidence for positive impact of international innovation on firms' financial performance. Working with more countries, or having a wider knowledge pool, is more important when firms would like to create more profit through international innovation. We also find that internationalization

of innovation would help firms to improve their innovation performance in terms of patent production. Experience in international innovation is more important in the process than other aspects.

Our study has three main limitations. One of the limitation is on the measurements. The measures of internationalization of innovations in this study are limited by the patent data we have. Measures based on more detailed patent data or other types of data can give us more insights into the question and produce more robust results. The measure for innovation performance is patent counts. Although this is a widely used measure of innovation, we cannot measure the quality or value of the innovation by simply using patent counts. The measure can be improved by adding quality components. For example, use citation-weighted patent counts.

Another limitation is on impact analysis. Increasing innovation outcomes are only one of the channels through which the internationalization of innovation affects the profitability of the firms. Other channels might include marketing, cooperation management, and environment risk. Only by combing with the effects of other channels can we completely show the effects of internationalization of innovation on firms' profitability. Therefore, further research can focus on the effects of other channels.

The other limitation is on the generalization of results. All our results are based on data of large pharmaceutical firms. Beside industry specifics, pharmaceutical industry is an R&D intensive industry as mentioned earlier. Therefore, the results might be different for other industries or for smaller firms.

In addition, for potential "incidental parameters problem" in the fixed effect Negative binomial regression models, we have noticed several options to deal with this type of problem. We will address this potential bias later on.

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APPENDIX A. FIRMS INCLUDED IN THE SAMPLE

Company name	Country (Headquarter)
Abbott	USA
Actavis	USA
Actelion	Switzerland
Adolor	USA
Allergan	USA
Amylin	USA
Zeneca	UK
Avanir	USA
Bausch & Lomb	USA
Bayer	Germany
Bristol-Myers Squibb	USA
Celgene	USA
Cephalon	USA
Cubist	USA
Cytogen	USA
Dusa	USA
Elan	Ireland
Endo	Ireland
Forest	USA
Genentech	USA
Glaxo, SmithKline	UK
Hospira	USA
ImmunoGen	USA
Inspire	USA
Ipsen	France
Isis	USA
Johnson & Johnson	USA
King	USA
Ligand	USA
Lilly	USA
Lundbeck	Denmark
Merck & Co.	USA
Merck KGaA	Germany
MGI	USA
Mylan	USA
Nektar	USA
Novartis	Switzerland

Novo Nordisk	Denmark
NPS	USA
Onyx	USA
Optimer	USA
Procter & gamble	USA
Pfizer	USA
Pharmion	USA
Protherics	UK
Questcor	USA
Regeneron	USA
Replidyne	USA
Roche	Switzerland
Sanofi	France
Schering	USA
SciClone	USA
Shire	Ireland
Solvay	Belgium
Tanox	USA
Targacept	USA
United Therapeutics	USA
Valeant	USA
Vernalis	UK
Vertex	USA
ViroPharma	USA
Wyeth	USA

APPENDIX B. ROBUSTNESS CHECK

B.1 Firm type

Model 1:

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
VARIABLES	pat	pat	pat	pat	pat	pat	pat	pat
	Negative Binomial RE	Negative Binomial FE	Negative Binomial RE	Negative Binomial FE	Negative Binomial RE	Negative Binomial FE	Negative Binomial RE	Negative Binomial FE
pstock	0.000843***	0.000824***	0.000845***	0.000826***	0.000842***	0.000820***	0.000589***	0.000592***
	(0.000180)	(0.000147)	(0.000280)	(0.000162)	(0.000160)	(0.000192)	(0.000123)	(0.000138)
L.rd_intensity	-0.00134	-0.00125	-0.00138	-0.00130	-0.00128	-0.00121	-0.00129	-0.00121
	(0.00323)	(0.00462)	(0.00271)	(0.00277)	(0.00263)	(0.00320)	(0.00214)	(0.00271)
L.ind1	-0.00230	-0.0112						
	(0.0464)	(0.0462)						
L.ind2			0.0900	0.0776				
			(0.0786)	(0.0911)				
L.ind3					0.202**	0.197**		
					(0.0939)	(0.0859)		
L.ind4							0.307***	0.286***
							(0.0804)	(0.0794)
L.sale_real	-2.12e-05	-2.65e-05*	-2.28e-05*	-2.78e-05*	-3.52e-05***	-4.09e-05***	-3.40e-05***	-3.82e-05***
	(1.36e-05)	(1.40e-05)	(1.30e-05)	(1.50e-05)	(1.21e-05)	(1.29e-05)	(1.28e-05)	(9.01e-06)
L.ma	-0.000931	9.55e-06	-0.000464	0.000285	-0.0108	-0.00980	-0.0117	-0.0101
	(0.0170)	(0.0164)	(0.0154)	(0.0150)	(0.0130)	(0.0139)	(0.0206)	(0.0171)
Constant	1.347***	1.388***	1.381***	1.419***	1.489***	1.538***	1.527***	1.559***
	(0.198)	(0.155)	(0.158)	(0.157)	(0.131)	(0.183)	(0.142)	(0.152)
Observations	606	604	606	604	606	604	606	604
Number of firms	56	54	56	54	56	54	56	54
Log-likelihood	-2369	-1984	-2367	-1983	-2356	-1973	-2349	-1967
Chi2	33.51	48.81	20.38	43.48	45.80	47.03	102.4	71.27

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

Note: For each indicator, the model is estimated using Poisson estimator Random Effect (RE) and Fix Effect (FE), and Negative Binomial Estimator Random Effect (RE) and Fixed Effect (FE). Robust cluster errors are reported in braces except for Poisson FE with robust standard errors. All constants are omitted. Log-likelihood test with null hypothesis that some arbitrary group of k coefficients in the model is equal to zero, are applied. The Wald test with null hypothesis that all the coefficients except constant are zeros, are applied.

Model 2

	(1)	(2)	(3)	(4)
VARIABLES	profit1	profit1	profit1	profit1
L.profit1	0.452***	0.424***	0.421***	0.373***
	(0.0821)	(0.0814)	(0.103)	(0.0916)
L.profit2				
L.profit3				
L.ind1	0.0409*			
	(0.0219)			
L.ind2		0.112***		
		(0.0352)		
L.ind3			0.103**	
			(0.0497)	
L.ind4				0.196***
				(0.0637)
L.ma	0.0124***	0.0105**	0.00997**	-0.00674
	(0.00443)	(0.00483)	(0.00411)	(0.00647)
firm_winner	0.0144	-0.000468	0.0231*	-0.0496*
	(0.0160)	(0.0174)	(0.0138)	(0.0280)
firm_slowstarter	-0.0704	-0.0433	0.0298	-0.0388
	(0.0464)	(0.0419)	(0.0443)	(0.0357)
firm_quickstarter	-0.0653*	-0.0451	0.0253	-0.0662
	(0.0353)	(0.0392)	(0.0590)	(0.0407)
Constant	-0.0291**	-0.0375*	-0.0767**	-0.0217
	(0.0148)	(0.0204)	(0.0331)	(0.0191)
Observations	929	929	929	929
Number of firms	61	61	61	61
Wald test (p-value)	0	0	0	0
AR(2) (p-value)	0.709	0.653	0.586	0.756
Hansen test (p-value)	1	1	1	1

Robust standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1 Notes: The models are estimated using the Arellano-Bond estimator by Arellano and Bond (1991) and implemented by STATA 13 by Roodmand (2009). Robust cluster errors (clustered by firm) are reported in braces. Robust clustered standard errors are implemented by STATA 13 Roger (1994). Year dummies were used in each model. Instrument sets of lagged depend variable (GMM style) and all other right-hand-side variables (IV style). The following tests are applied: 1. The Hansen test as a test of erogeneity and validity of instrument subsets; (Since we are using robust clustered standard errors, Sargan test is inappropriate.) 2. AR(2) test as a test for second-order serial correlation, required by suing the Arellano-Bond estimator; 3. The Wald test with the null hypothesis that all the coefficients except the constant are zero. All tests are reported by their p-values for convenience.

B.2 Including all indicators

Model 1

	(1)
VARIABLES	pat
pstock	0.000645***
	(8.74e-05)
L.rd_intensity	-0.00208
	(0.00196)
L.ind1	0.0534
	(0.0489)
L.ind2	-0.00283
	(0.0646)
L.ind3	0.0674
	(0.110)
L.ind4	0.179***
	(0.0542)
L.sale_real	-4.87e-05***
	(7.97e-06)
L.ma	-0.0209
	(0.0193)
Observations	606
Number of firms	56
Log-likelihood	-4781
Chi2	2624

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Model 2

	(1)
VARIABLES	profit1
L.profit1	0.332***
	(0.111)
L.ind1	-0.0141
	(0.0226)
L.ind2	-0.00246
	(0.0695)
L.ind3	0.0576
	(0.0486)
L.ind4	0.146
	(0.0893)
L.ma	-0.00552
	(0.00867)
L.emp	-0.000448
	(0.00161)
Constant	-0.0493
	(0.0680)
Observations	674
Number of firms	56
Wald test (p-value)	0
AR(2) (p-value)	0.325
Hansen test (p-value)	1

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

CHAPTER 2. IMPACT OF UNCERTAINTY ON INNOVATION AND INVESTMENTS IN THE PHARMACEUTICALS INDUSTRY

2.1 Introduction

The theoretical and empirical literature on uncertainty reveals that important aspects of firms' decisions can be affected by uncertainty about market conditions. The literature on uncertainty has investigated that uncertainty could arise from a wide range of factors, including demand, prices, input costs, cash flow, project returns, technology, and policies. The effects of uncertainty have also been studied extensively in the literature, especially for the effects of uncertainty on investments. Theory on this topic identifies four channels through which uncertainty may affect firms' investments. These include the real options, which predicts that uncertainty increase the value of waiting for the irreversible capital (Pindyck, 1991; Dixit, 1992; Dixit & Pindyck, 1994); information asymmetry between lenders and borrower, which predicts that under uncertainty, the credit may flow to specific categories of business (Greenwald and Stiglitz, 1990); risk aversion of firms (Appelbaum and Katz, 1986; Hartman, 1976); and the convexity of the marginal product of capital, which predicts that increases in price uncertainty may increase a firm's current investment, due to the convexity of the marginal revenue product of capital function with respect to price (Abel, 1983). To summarize, despite the last channel, all the other three channels investigated recently have predicted a negative relationship between uncertainty and investments. As we will discuss in detail in the next section, most empirical studies on the effects of uncertainty on firm investments have been using disaggregated U.S. and

European manufacturing data and have similar results that uncertainty generally decrease investments.

As a particularly relevant example of irreversible capital, R&D expenditure is also under the influence of uncertainty. As uncertainty increases, firms might choose to wait for new information instead of hiring research personnel and purchase research facilities as planned. Therefore, uncertainty could also decrease firms' R&D expenditure. As innovation is the output of R&D expenditure, although the results of research projects are often unpredictable, decrease in input of innovation would definite affect the output. Therefore, from this point of view, the relationship between uncertainty and innovation should also be negative.

Receiving the literature on uncertainty, the impacts on investment is the topic that has the longest discussion. The core models and main theories (MacDonald and Seigal, 1986; Dixit, 1989; Dixit and Pindyck, 1994, etc.) in the uncertainty literature all come from literature examining the impact of uncertainty on firms' decision variables related to investment. The work on R&D expenditure and patent were down much later. Therefore, in this paper, the objective is to examine the effects of uncertainty on first on investment, then R&D expenditure, and innovation, respectively, using the data on firms in the pharmaceutical industry. The paper is organized as the following: Section 2 summarizes the related literature on the effect of uncertainty on investment, R&D expenditure, and innovation, and raise the research question; Section 3 discusses the data sources and treatment; Section 4 describes the definition of the measures for uncertainty; Section 5 discusses the empirical strategies towards the research questions; Section 6 discusses the estimation results; Section 7 concludes the study and discusses about possible limits.

2.2 Literature Review

As mentioned earlier, the literature on the impacts of uncertainty started and are centered at the impact on investment. Then studies on the impact on R&D expenditure and innovation were built on the theory and empirical studies on the impact of uncertainty on investment. As R&D expenditure is a type of investment, at the meantime, the input for innovation, starting from the impacts on investment allow us to start from general theories of uncertainty before going into specific empirical impact analysis. Therefore, in this section, we discuss three topics related to uncertainty and innovation. We start with a discussion of the relationship between uncertainty and general investment. We then will narrow down to R&D investment. In the last part, we discuss the relationship between uncertainty and innovation output. As R&D investment is a type of investment and the input for innovation output, the three topics are closely related. As the theoretical models of uncertainty and investment form the base of the discussion, we start with investment. Discussion on each theoretical model is followed by relevant empirical studies.

2.2.1 Uncertainty and investment

An extensive literature focuses on the relationship between uncertainty and investment. In this section, we discuss three main theoretical models related to real-option, financial constraints driven by information asymmetry, and risk-preferences.

2.2.1.1 Real-options

A considerable literature has explored the relationship between uncertainty and investment under the real-options framework. In the theoretical literature, McDonald and

Siegel (1986), Dixit (1989), and Dixit and Pindyck (1994) assume that costs remain unchanged, but market demand fluctuates, therefore the uncertainty is from the demand side and sunk costs imply an option value of waiting. The simulation results in Dixit (1989) and Dixit and Pindyck (1994) show that even small amounts of uncertainty are sufficient to depress investment and entry.

Pindyck (1993) examines the effect of uncertainty from costs, including input costs and technical costs. The simulation results show that the optional capital stock decreases with input cost uncertainty, but increases with technical uncertainty. Since the optional capital is more sensitive to input cost uncertainty, they have similar results to those obtained under demand-side uncertainty that negative effects from the input cost uncertainty dominants the positive effects from technical uncertainty, therefore, the overall effect is negative.

There are also other models under the real-options framework. For example, Kulatilaka and Perotti (1998), Folta and O'Brien (2004), Oriani (2007), and Oriani and Sobrero (2008) found an inverted U-shaped relationship between demand uncertainty and R&D investment, because frontier technologies changes in future periods make firms consider waiting for technology evolvement before increase R&D investment to create an option to switch.

2.2.1.2 Information asymmetry and financing constraints

Greenwald and Stiglitz (1990) investigated how informational asymmetries between borrowers and lenders can tighten financial constraints for certain types of borrowers. They argued that increased uncertainty about profitability could increase the risk of bankruptcy,

and firms relying primarily on credits cannot issue equity to absorb the risk, therefore, they can only respond by lowering their investment.

Delli Gatti et al. (2003) extended the framework of Greenwald and Stiglitz (1990). They showed that if the financial conditions can affect capital investments and entry and exit, greater uncertainty would widen the informational asymmetries, increase the likelihood of bankruptcy, exacerbates financing constraints, and affect firms' decision on a wide range of variables including investments.

In contrast to the agency-based models mentioned above, Campbell and Cochrane (1999) demonstrated that greater macroeconomic uncertainty leads to countercyclical variation of volatility and risk premia, which results in a negative correlation between uncertainty and key decision variables such investment.

2.2.1.3 Risk-preferences

One of the oldest explanation on the relationship between uncertainty and investments is based on risk preferences. There are two strands of literature on this topic. The traditional one follows the assumption that risk and return are positively correlated. Therefore, firms with greater risk aversion will produce less and changing their input-mix (Sandmo, 1971; Hartman, 1972, 1973, 1976; Appelbaum and Katz, 1989; Gul, 1991; Aizenman and Marion, 1999). Ghosal (1991, 1995) examined these models empirically, finding that greater uncertainty alters the input-mix and results in lower capital-labor ratios.

The other strand of literature challenges the traditional linear relationship between uniform risk-references and decision-making. For example, Bowman (1980, 1982) raised

a negative risk-return relationship in some industries. Based on Kahneman and Tversky's (1979) prospect theory, this line of literature complicates the predictions on the effects of uncertainty on investment.

In summary, the literature on the effect of uncertainty on investment generally finds negative effects. As the purpose of this paper, we would also test the hypothesis:

Hypothesis 1: Uncertainty is expected to have a negative effect on investment.

2.2.1.4 Uncertainty and Innovation

In the theoretical analysis of the relationship between uncertainty and R&D investment, Abel et al. (1996) demonstrated that investment decisions involve the following two options. The reversibility option captures the value of opportunities and costs when disinvestment happened in the future, which increases the incentive for current investment when future returns are uncertain. On the other hand, the expandability option captures the value of opportunities and costs when investment happened in the future, which decreases the incentive for current investment when future returns are uncertain. Thus, their model shows that the overall effect of uncertainty on investment depend on the nature of the options, which is partly determined by the type of the capital investment. The R&D investment we discuss in this paper is typically considered as investments that have very small reversibility, but considerable expandability. Since R&D investments are mainly used for the salaries of R&D personnel, setting up and running research laboratories, and purchases of equipment, the R&D investments are often characterized as largely irreversible (e.g. Dixit and Pindyck, 1994). Therefore, for R&D investments, the negative effects from expandability would dominant under uncertainty.

Bloom (2007) explores this topic by extending existing models to incorporate time varying uncertainty. He showed that high uncertainty reduces the responsiveness of R&D to changes in demand and increase the persistence of R&D over time. The main purpose of Czarnitzki and Toole (2011) was to investigate the mechanism through which patents stimulate R&D investment. Part of their finding using the data of German manufacturing firms from 1995 to 2001 is that firm-level R&D investment decreases in response to higher levels of uncertainty. Summarizing the literature on the effects of uncertainty on firms R&D expenditure, we can find that they all have investigate the following hypothesis.

Another strand of literature investigates the relationship between competition and R&D investment incorporating uncertainties in the models, which typically known as patent race theory. Early work on the patent race theory using one-step static models, focuses on the effects of technologies uncertainty, which refers to the differences in efficiency and timing of the invention discovery process (Dasgupta and Stiglitz, 1980; Gilbert and Newbery, 1982). There are also studies focusing on dynamic uncertainty alone, which refers to the change in firms' incentives to Invest in R&D as the race unfolds (Fudenberg et al., 1983; Harris and Vickers, 1985). Later work combines the two types of uncertainty into the patent races under dynamic multi-stage structure (Grossman and Shapiro, 1987; Harris and Vickers, 1987). However, empirical evidence on the patent race theories has been inconclusive. (Zizzo, 2002)

Summarizing the literature, we examine the relationship of uncertainty and R&D investment through the following hypothesis.

Hypothesis 2: Uncertainty is expected to have a negative effect on R&D investment.

Theoretical discussion on the relationship between uncertainty and innovation has been going on for a long time. There are two strands of literature tied to this. One is the debate of the sign of the effect of uncertainty on innovation. A traditional argument is that the uncertainty in the market is likely to compel incumbent firms to secure their position through innovation (e.g. Myers and Marquis, 1969, Miller and Friesen, 1982, Özsomer et al., 1997, Bhidé, 2003, Freel, 2005), while the converse argument is consistent with our discussion of negative effect of uncertainty on R&D investment, that since the uncertainty would lead to decrease in R&D investment, so would it lead to decrease in innovation as the output. The other strands of literature discuss the problem by reversing the two sides, arguing that innovation create uncertainty. The most famous argument is the "Creative Destruction" by Joseph Schumpeter, that innovation would bring revolutionary economic changes, which leads to uncertainty. Therefore, due to the complexity of the relation between uncertainty and innovation, it is hard to predict the sign of the effect.

Compared to the extensive empirical studies on the effects of uncertainty on R&D investment decision, only limited number of empirical studies investigate the effect of uncertainty on patent out. Freel (2005) extended the investigation on the effects of uncertainty on innovation to differences in the effects for firm size and industry. From a survey of English small- and medium-sized enterprises, he found that for manufacturing industry, higher levels of innovation are associated with higher perceptions of supplier uncertainty, while for service industry, higher levels of innovation are associated with higher perceptions of human resource uncertainty. Here, we follow the discussion on the effect of uncertainty on investment. Since innovation, measured as patents here, is

generally considered to be the output of R&D investment (Griliches, 1980, Pakes, 1985, we expected that:

Hypothesis 3: Uncertainty has positive effects on innovation.

2.3 Data

To examine the effects of uncertainty on firms' investments, R&D, and patents, we focus on the pharmaceutical and biotechnology industries, defined by North American Industry Classification System (NAICS): 325411 – Medicinal and Botanical Manufacturing; 325412 – Pharmaceutical Preparation Manufacturing; and 541711 – Research and Development in Biotechnology. For convenience, in this paper, we refer firms in both industries as "pharmaceutical firms." As firms in these industries are among the most intensive in R&D and patenting, and significant capital investments, they serve as an ideal sample to study the effects on uncertainty.

2.3.1 Sample

We include all top pharmaceutical firms in recent years. To get a listing of these firms, we referred to several online sources, including Current Partnering, PMLiVE, Contract Pharma and Wikipedia. Lists from these sources are all based on financial data after 2007 and include no more than 50 firms. We then combined them into a final list of big pharmaceutical firms in the U.S. and Europe. The top firms listed and used in this study include 172 firms worldwide. Since the study focuses on U.S and European firms and there are firms that we cannot find financial information, our final sample drops to 63 firms. The list can be found in Table A1 in the Appendix.

2.3.2 Patent data

Patents are awards to firms' research activities and are often linked to new technologies introduced the market. Following the common practice in the literature, we use patent numbers as a measure of innovation performance in this paper. Pharmaceutical industry, overall, has a very high patenting rate and patents are critical to a firm's success (Scherer at al., 1959; Mansfield, 1986; Levin et al., 1987; Coad and Rao, 2008; Helmers and Roger, 2011; etc.). According to a survey by researchers at Carnegie-Mellon University in 1994 (Cohen et al., 2000), pharmaceutical firms reported that 78% of their business units filed for patents. In the literature, both patent applications and patent grants are used to count patent numbers. Due to the patenting process, there is a considerable time lag from filing to granting. Therefore, the patent application[9] is a better measure of a firm's innovation outcome.

Our patent data are from PubWEST, which includes patents from United State Patent and Trademark Office (USPTO), European Patent Office (EPO), and Japan Patent Office (JPO)[10] . We include only USPTO and EPO patents under corresponding pharmaceutical categories defined by IPC (International Patent Classification), which are A61K (Preparations for medical, dental, or toilet purposes) and C12N (Micro-organisms or

[9] Generally, not all patent applications will be granted. One of the common reasons for the failure is that the patent authority does not think the invention is not innovative enough, so the patents grant is believed to be a better measure of innovation. To accommodate both the quality of the invention and the timing of the process, we use successful patent applications in our dataset.

[10] The JPO data provided by the PubWEST has only basic information with missing values for important fields, such as patent class, inventors, and the address of the inventors, so the JPO data is excluded from the sample. The other reason for the exclusion is that patent laws in U.S. and Europe are similar, while patent laws in Japan is much different. Therefore, every firm in our sample has patents from its home patent authority, and the patents are regulated by similar patent laws. These factors are very important for international patenting and international innovation.

enzymes; Compositions thereof; Propagating, preserving, or maintaining micro-organisms; Mutation or genetic engineering; Culture media).

To include all the patents for each firm, we made queries using both the names of the parent company and its subsidiaries. Public listed firms in U.S. are required to submit filings every year about their finance and operation. Therefore, 10-K is the most updated source for firm's subsidiaries. To simplify the procedure, we only use the most recent one, the 2012 10-K for U.S. firms.[11] We referred to the 2012 10-K of most firms publicly traded in US for their subsidiaries information. Subsidiaries information for other firms is from Mergent Online. We also manually update the ownership of the patents for some firms for years after mergers and acquisitions.

2.3.3 Economic and Financial Data

We collected the annual accounting data of publicly-traded pharmaceutical firms from the Compustat database.[12] Data on firms traded in USA and Canada are from Compustat North America, while data on other publicly traded firms are from Compustat Global. After matching firms on our list with those in the Compustat in the period from 1990 to 2010, we have 63 firms left in the final sample.[13]

2.3.4 Other Data Issues

[11] Due to the simplification, we are not able to have highly-accurate subsidiary information for each firm in each year. We assume that the change in subsidiaries are very small from year to year and firms will always keep patents under the name of the parent firm or existing subsidiaries unless they would like to sell their patents together with a subsidiary, which we do not capture in our data.
[12] R&D data from Compustat include a lot missing and abnormal values, therefore, we instead collected R&D expenditure data from the annual financial reports provided by MergentOnline.
[13] This number is comparable Roberts (1999), which had a sample of "42 firms that were in the top 40 (according to U.S. pharmaceutical sales) in any one of the sampled year", from 1977 to 1993.

Since our dataset comes from different data sources, we did more work to consistently combining data from different data sources together. Even though the two datasets from Compustat and PubWEST can be combined using corporate registration and identification information, inconsistences in year coverage exist between the two datasets. In other words, the starting year for a firm's patent data, the starting year for a firm's financial data, and the official or legal starting year for a firm might be different. After our manual treatment based on information from Bloomberg, Mergent Online, firm's own websites, and Compustat, a firm might have a different starting year from the starting year of the study period for one of the following two reasons: (1) the firm was formed by merging with another firm; (2) the firm was separated from another firm (spin-off). Likewise, a firm's ending year might be different from the ending year of the study period because it was later acquired by another firm.

For patent data from PubWEST, some patents with US inventors have missing values in the inventor country field, but have values in the inventor state field. Therefore, the country information used in this study was in fact a combination of these two fields.

2.4 Methodology

2.4.1 Measures of uncertainty

Uncertainty could arise from many factors. Economists have been studying factors including demand (Dixit 1989; Dixit and Pindyck, 1994), input costs (Pindyck, 1993), technical factors (Pindyck, 1993) and policy factors (Pindyck, 1993; Dixit and Pindyck,

1994, 1995).[14] The empirical literature on uncertainty at firm level has used measures primarily based on profit, stock returns, productivity, or subjective forecasts from surveys (Jurado et al, 2015). Here we build our measures of uncertainty based on three of the most commonly used variables: sales, stock price, and profit. We use two most commonly-used methods to build the measures: using the residuals from forecasting equations and using the conditional variance.

Measure 1: Sales-based measure

First, we assume that firms predict future sales based on their own past sales and GDP growth, as shown in the specification below. Therefore, the predicted values represent the forecastable component, while the residuals represent the unpredictable, i.e. uncertainty. Using the residuals of the forecasting equations and using the conditional variance to construct uncertainty measures is common in the literature. Lensink et. al. (2001), for example, include a comprehensive overview of this literature and alternative frameworks that have been used in the literature for measuring uncertainty.

The sales used here is real sales adjusted for inflation by PPI (Producer Price Index) for the pharmaceutical industry from Bureau of Labor Statistics. GDP as a gross measure of the whole economy, captures all the demand and supply effects, therefore, changes in GDP provide a good measure of macroeconomic uncertainty. Uncertainty measures based on GDP growth in different forms, have been widely used in the literature (Driver et al., 2005; Asteriou and Price, 2005; Bloom, 2009). Since the firms in our sample is all big

[14] There are also many studies about sources of uncertainty from the management point of view. Priem et al (2002) had a comprehensive review of studies on this topic and brought up a classification of uncertainty sources, which include “international competitive advantage”, “industry competition”, “production costs”, “human resources”, “government”, “societal change”.

multinational firms, the predication of the future economy of the firms should be based on the world-wide economic changes. Therefore, we used the OECD-wide GDP in the regression. Here we use the growth rate of GDP, which have been commonly used by the literature (e.g. Driver et al., 2005, Asteriou et al., 2005, and Bloom, 2009). The sales are the real sales adjusted for inflation by GDP deflator.

We specify our forecasting model as following. As the baseline, we first use a second-order autoregressive AR(2), specified as following:

$$Sales\ Growth_{i,t} = \gamma + \alpha_1 \cdot Sales\ Growth_{i,t-1} + \alpha_2 \cdot Sales\ Growth_{i,t-2} + \beta_1 \cdot GDP\ Growth_{t-1} + \beta_2 \cdot GDP\ Growth_{t-2} + \varepsilon_{i,t} \quad (4)$$

Then the predicted values represent the forecastable component. The residuals:

$$\widehat{\varepsilon_{i,t}} = Sales\ Growth_{i,t} - \gamma - \widehat{\alpha_1} \cdot Sales\ Growth_{i,t-1} - \widehat{\alpha_2} \cdot Sales\ Growth_{i,t-2} - \beta_1 \cdot GDP\ Growth_{t-1} + \beta_2 \cdot GDP\ Growth_{t-2} \quad (5)$$

represent the unforecastable component. Since (ε_t)ˆ can be either positive and negative, we use ε_t^2 as the measure of uncertainty for year t. Our data start from 1990, but we lost two years of observations due to taking lags. The measure starts from 1992, so does our estimation.

An alternative way to use the residuals is to use the standard deviation of the residuals over five-year overlapping periods: 1992-1996, 1993-1997, …, 2006-2010. The standard deviation of the residuals over first five-year period 1992-1996 serve as the observation on uncertainty for the year 1997, so the estimation using this measure starts from 1997. Since the second measure have similar estimation results, we only show the results of the first measure in the paper, which we label as “UNCER1”.

Measure 2: Stock price-based measure

In a country with active financial stock market, the stock price of a firm is assumed to capture the possible economic changes related to the firm forward looking of investors, or business confidence, therefore, the volatility of the stock price is a good measure of the broad uncertainty faced by the firm. Stock price have been used to construct measures of uncertainty in many studies (e.g. Bloom, 2009; Bloom et al., 2007; Greasley and Madsen, 2006, and Stein and Stone, 2010). Here we scale the stock price divided by a stock market index. As mentioned earlier, to capture the uncertainty from the global market, we need a stock market index, which is based on the stocks from firms worldwide. Here we use the Dow Jones Global Index, which is based on more than 5500 companies around the world. Therefore, the uncertainty measure based on stock prices is calculated by the within-year variance of the following monthly (m) ratio:

$$\frac{Stock\ Price_{im}}{Market\ Index_{m}} \tag{6}$$

where m denotes a specific month of the year, and I denote a specific firm. This procedure of within-year variance is common in the literature (e.g. Lensink et al., 2001). Since this variance is calculated from each year, the uncertainty measure is available for the whole sample period, from 1990 to 2010, and the estimation using this measure starts from 1990.

Using the stock price and index, we also employ the forecasting model method[15] and get a measure from the residuals, Similar to UNCER1, this measure also starts from 1992.

[15] The forecasting model for the stock price does not include GDP growth variables.

Since the second measure using the forecasting model have the similar estimation results as the first measure using within-year variance, only the estimation results of the first measure are shown and discussed in the paper.

Measure 3: Profit-based measure

As sales, firms' profit also fluctuates over the business cycle. Unpredictable component of the profit change is defined as uncertainty here. Using profit to measure uncertainty is consistent with prior work (Aizenman and Marion, 1999; Ghosal, 1991, 1995, 1996; Ghosal and Loungani, 1996, 2000; Huizinga, 1993; Leahy and Whited, 1996). We employ the same forecasting model[16] using profit growth rate to get another measure of uncertainty, which we label as "UNCER3". The profit we use here, is the net profit margin, which equals net profit divided by sales. The uncertainty measures based on sales and profits measure similar uncertainty from the product market. The estimation results of the two types of measures are also close. We include only the measure based on sales, UNCER1, in the estimation part, and put the estimation results in the Appendix.

Summary statistics for the three measures are shown in Table 7.

Table 8 - Uncertainty Measures

Variable	Obs	Mean	Std. Dev.	Min	Max
uncer1	810	2.418592	22.28023	0	505.864
uncer2	880	0.041208	0.141657	0.000227	1.918048
uncer3	741	524.6574	8240.618	0	216805.2

[16] The forecasting model for the profit does not include GDP growth variables.

2.4.2 Estimation Strategy

Substantial literature involves estimation of the effects of uncertainty on firms' decision variables, including investments, employment, inventories, R&D and so on. Following the popular practices in the literature, we employ different methods for estimating the effects of uncertainty: (1) dynamic panel model for Hypothesis 1 and Hypothesis 2, (2) negative binomial and Poisson estimator for Hypothesis 3.

Firms' investment and R&D expenditures are important decision variables. A substantial literature has been on estimation of the effects related to firms' decision variables. Besides investment and R&D expenditure, there are also employment, inventory, and other variables (e.g., Eisner and Strotz, 1963, Sargent, 1978, Kennan, 1979, Hendry et al., 1983, and Jorgenson, 1986). Following the literature, we use a partial-adjustment framework to structure our empirical specification. The partial-adjustment framework model is based on a quadratic cost-minimizing framework where firms minimize disequilibrium and adjustment costs, when choosing optimal adjustments to the decision variable. The disequilibrium costs arise from loss of profit because the relevant decision variable is at a sub-optimal level. The adjustment costs arise from the firm's temptation to align the actual quality of the relevant decision variable to its optimal level. Therefore, higher disequilibrium costs would motivate a firm to adjust the relevant decision variable faster, while high adjustment costs would motivate a firm to adjust more smoothly and slowly. In other words, the disequilibrium costs and adjustment costs act in opposite directions. This implies that the actual speed of the adjustment will be a weighted-average of the two countervailing forces.

Let a firm's decision variable be Y, and Y* be the optimal (or equilibrium) value of Y. The partial-adjustment model is given by:

$$Y_t - Y_{t-1} = \lambda(Y_t^* - Y_{t-1}) \tag{7}$$

This means that the actual intertemporal adjustment of Y, $(Y_t - Y_{t-1})$ is typically a fraction λ $(0 \leq \lambda \leq 1)$ of the desired intertemporal adjustment $(Y_t^* - Y_{t-1})$. Thus, λ denotes the speed of response.

After rewriting, we have:

$$Y_t = (1 - \lambda)Y_{t-1} + \lambda Y_t^* \tag{8}$$

This means that the actual quality of Y is affect by both the last value of Y, and the optimal value of Y at time t. Y* is generally private information to the firm, therefore, cannot be observed from the outside. We model Y* as a function of a list of driving variables, denoted by X, and uncertainty, that is:

$$Y^* = f(\boldsymbol{X}, UNCER) \tag{9}$$

where UNCER denotes uncertainty.

After combining with the previous equation and rearranging, and including firm fixed-effects and year-time dummies, our estimation specification is:

$$Y_{i,t} = \alpha Y_{i,t-1} + \boldsymbol{X'\beta} + \gamma UNCER_{i,t-1} + \gamma_i + \delta_t + \varepsilon_{i,t} \tag{10}$$

where Y is net investment for Hypothesis 1, and R&D intensity for Hypothesis 2. The lagged variable, Y_(t-1) also act as an important control variable here. It controls at least two types of factors: (1) possible persistence in the intertemporal path of Y; (2) omitted

firm-specific time-varying factors that might affect the intertemporal path of Y. Therefore, our models are dynamic panel models. Since the lagged dependent variable is necessarily correlated with the idiosyncratic error, strict erogeneity in the regression is violated. Commonly used static panel data techniques such as fixed effects estimators would be inconsistent. To deal with this problem, we used the most popular Arellano-Bond estimator for the dynamic panel model, which is a generalized method of moments (GMM) estimator. Investment is scaled by the beginning-period capital stock, that is, I_t/K_{t-1}. The investment, I is the "Capital Expenditures on Property, Plant and Equipment Schedule V" (Compustat item 30). The capital stock, K is the computed from the "Property, Plant and Equipment – Total (Gross)" (Compustat item 7) following the method in Hall (1990). The capital stock, K, is deflated by the capital investment deflator for "325 Chemical Products" industry reported in the "Capital and Related Measures from the Three-Digit Database, 1987-2015" from Bureau of Labor Statistics. The deflator is applied at the calculated average age of the capital sock, based on the ratio of total accumulated depreciation (Compustat item 196) to current depreciation (Compustat item 14).[17]

The depreciation rate for all types of assets for the U.S. "24 Chemicals and Chemical" industry from the EUKLEMS database (November 2009 release). Thus,

$$K_t = capital\ stock_t(1-\delta)^{age_t}/deflator_t \tag{11}$$

where δ is the depreciation rate, age is the average age of the capital stock.

[17] The calculation of the average capital age follows Brynjolfsson and Hitt (2003) and Bugamelli and Pagano (2004), which are slightly different from the method in Hall (1990). That is, $age = \min(age\ of\ the\ firm, 3 - year\ average\ age\ of\ the\ capital\ stock)$.

R&D intensity is the real R&D expenditure scaled by real sales. UNCER is uncertainty. X is the vector of control variables. Here, we include sales growth rate as the control for firm size, and year dummies. Investment data are scaled by capital stock. Sales data are adjusted to base year 1990, using Producer Price Index from U.S. Bureau of Labor Statistics for the pharmaceutical industry.

The patent production function is widely used in patenting studies (e.g. Hall and Ziedonis, 2001; Hu and Jefferson, 2009). We specify our augmented patent production function as:

$$E(PAT) = \exp(\boldsymbol{V'\beta_V} + \boldsymbol{UC'\beta_U}) \tag{12}$$

where PAT is the count of patent applications[18], the vector V stands for traditional explanatory variables in the patent production function, including R&D expenditures, firm size, research capability and other variables. UC is the uncertainty faced by the firm.

Taking logarithm for both sides and specifying our estimation function as:

$$\begin{aligned}\ln(PAT_{i,t}) = \beta_0 + \beta_1 UNCER_{i,t-1} + \beta_2 \ln(R\&D_{i,t-1}) \\ +\beta_3 Sales\ Grouth_{i,t-1} + \gamma_i + \delta_t + u_{i,t}\end{aligned} \tag{13}$$

where UC is still the measure of uncertainty, and u is the error term. [19]

Since the dependent variable is patent counts, we employ Poisson and Negative Binomial regression models, which are commonly used in studies of patent output (e.g.

[18] Since PAT = 0 occurs, we have all the PAT added by 1, so PAT starts from 1, even though the firm did not file for a patent in that year. This would not affect the results much, because firms in our sample are all big firms in the industry with high volume of patent applications. The mean of PAT in our dataset is about 70, and it has a variance of 132.

[19] Since zero values were found for some firms at some years, we added 1 to PAT, therefore, the patent number start from 1, and are suitable for logarithm.

Henderson and Cockburn, 1996; Hall and Ziedonis, 2001; Penner-Hahn and Shaver, 2005; Hu and Jefferson, 2009). For the fixed effect Negative Binomial regression models, there is a potential "incidental parameters problem". We have noticed several options to deal with this type of problem. We will address this potential bias later on.

We include R&D expenditure as the input for innovation. R&D expenditure is a long-term investment, which takes time to have impacts (Barker and Mueller, 2002). However, it is generally difficult to identify the lag structure of the impacts. Moreover, the lag structure is likely to be different among firms and projects. As discussed in Hall and Ziedonis (1995), due to "the high within-firm correlation of R&D spending over time", the estimation results among R&D variables with different lag periods are "roughly the same". So here we use one-year lagged R&D to be consist with other variables in the model. We measure research capability as firms' patent stock for the previous three years. We also include sales as the control for firm size.

We use clustering of errors for all models in the paper. For panel data, where observations can be grouped into clusters, model errors might be uncorrelated across cluster but correlated within cluster, therefore, controlling for within-cluster error correlation is needed. Failing to control for within-cluster error correlation can lead to misleading standard errors, with narrow confidence intervals, large t-statistics, and low p-values. (Cameron and Miller, 2015). Therefore, clustering of errors is applied to every model and estimation as feasible.

For linear regression model, the traditional way to control for clustered errors is to estimate a model specified for the within-cluster error correlation, and then estimate the

original model by feasible generalized least squares (FGLS) rather than ordinary least squares (OLS). However, the model only generates valid statistical inference, and more efficient estimates under the strong assumption that the model for within-cluster error correlation is correctly specified. (Cameron and Miller, 2015). A more recent method to control for clustered errors is to estimate the regression model limited or no control for within-cluster error correlation, and then obtain "cluster-robust" standard errors. For the fixed effects estimator in linear panel models, the cluster-robust standard errors are provided by Arellano (1987). The method was incorporated into Stata by Rogers (1994). When using the Arellano-Bond estimator, it is required to test whether the remaining error U_it is serially correlated. Generally, including fixed effects at cluster level does not control for all the within-cluster correlation of the errors. It is standard to test whether it is sufficient to estimate without cluster-specific fixed effects. We will discuss these tests in the estimation part. Even though pharmaceutical firms in our sample are all top firms in the same industry, they still vary greatly in size, profitability, and business lines. Therefore, we do cluster by firms.

Table 9 - Variable List

Variable Name	Name	Definition
INV	Investment	Investment scaled by the beginning-of-period capital stock
rd_real	R&D in real values	R&D spending adjusted by GDP deflator for OECD countries (base year 2010)
rd_intensity	R&D intensity	R&D spending divided by sales
sale_real	Sales in real values	Sales adjusted by GDP deflator for OECD countries (base year 2010)
sale_growth	Sales growth rate	The growth rate of sales in real values

Table 10 (continued).

gdp_oecd	GDP of OECD countries	The gross domestic product (GDP) for OECD countries
gdp_growth	The growth rate of GDP in OECD countries	The growth rate of GDP for OECD countries
PAT	Patent application counts	Counts of patent applications filed by a firm in a certain year
pstock	Patent stock	The sum of patent application counts in the last three years as the measure for research capability
UNCER1	Uncertainty measure based on sales-growth	Created from the error term of the auto regression of sales growth rate (including GDP growth rate in the regressors).
UNCER2	Uncertainty measure based on stock price	Standard deviation of the 12-month ratio of stock price for a certain firm to market index
UNCER3	Uncertainty measure net profit margin	Created from the error term of the auto regression of the net profit margin

Note: Lagged variables are not listed here. Lagged variables are simply the previous values of the variables listed here and are named by adding "L." in front of the original variables. For example, L.sale_growth is the lagged value for sale_growth, i.e. the previous value of sales growth rate. If it is the two-year lagged, then the variable would begin with "L2.".

Definitions for all variables are listed in Table 8. Table 9 shows the summary statistics for our data. Patent numbers show considerable between-firm and within-firm variation. As a result, patent stock the measure of research capability, also varies considerable across firms and within a firm over time. For the three measures of uncertainty, they also have considerable variance. Note they also have different ranges which makes the interpretation of their coefficients different. Uncertainty measure three generally has better correlation with other variables. R&D expenditure naturally has high correlation with investments and sales. Patent numbers correlate more with R&D expenditure, then with sales.

Table 11 - Summary Statistics

Variable	Mean	Std. Dev.
pat	70.63862	132.0902
pstock	227.1176	409.5573
rd_real	994785	1793006
rd_intensity	4499.957	31417.53
INV	0.345604	0.487325
$sale\_growth_{t-1}$	0.651609	3.450943

2.5 Estimation Results

2.5.1 Uncertainty and Investment

Estimation results for Hypothesis 1 are shown in Table 3. The specification for each model is the same, just with different uncertainty measures. We include lagged invests, current and previous period uncertainty measures, and current and previous period sales growth rate. The positive and significant coefficient on lagged investment statistically confirms the persistent behavior of investment, which is known as lagged investment effect. Only the previous period sales growth rate has a significant coefficient, which shows a statistically significant and positive impact on investment. For Model 1, the uncertainty measure UNCER1 only has significant coefficient for its lagged variable. The impact of uncertainty measured by UNCER1 is small in magnitude and negative. The impact of lagged UNCER2 is also negative, but insignificant. Despite the difference in the significance in the coefficients, all the models succeed in the tests of second-order autocorrelation and Sargan-Hansen J test of overidentification restrictions suggesting the validity of the instruments.

Table 12 - Estimation Results – Model 1

	(1)	(2)
VARIABLES	inv	inv
L.inv	0.278**	0.215**
	(0.118)	(0.0891)
L.uncer1	-0.00291**	
	(0.00135)	
L.uncer2		-0.0704
		(0.0550)
L.sale_growth	0.0372**	0.0133*
	(0.0188)	(0.00759)
Constant	0.183***	0.255***
	(0.0561)	(0.0498)
Observations	662	752
Number of firms	56	56
Wald test (p-value)	2.16e-10	1.54e-08
AR(2) (p-value)	0.837	0.978
Hansen test (p-value)	1	1

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Notes: The models are estimated using the Arellano-Bond estimator by Arellano and Bond (1991) and implemented by STATA 13 by Roodmand (2009). Robust cluster errors are reported in braces. Robust clustered standard errors are implemented by STATA 13 Roger (1994). Year dummies were used in each model. Instrument sets of lagged depend variable (GMM style) and all other right-hand-side variables (IV style). The following tests are applied: 1. The Hansen test as a test of erogeneity and validity of instrument subsets; (Since we are using robust clustered standard errors, Sargan test is inappropriate.) 2. AR(2) test as a test for second-order serial correlation, required by suing the Arellano-Bond estimator; 3. The Wald test with the null hypothesis that all the coefficients except the constant are zero. All tests are reported by their p-values for convenience.

2.5.2 Uncertainty and Innovation

Since R&D expenditure is a special type of investments, uncertainty should have similar effects on R&D expenditure as on investments. The model specification is the same as the model for investment. However, the estimated impact of uncertainty on R&D spending is mixed. For UNCER1, the current period uncertainty has significant negative impact on R&D spending, while the lagged uncertainty only has an insignificant negative coefficient. The R&D spending shows significant positive persistency. For sales growth

rate, only the two-period lagged sales growth rate affect the R&D spending positively. The estimation results for UNCER2 are generally insignificant. All models in this table pass the autocorrelation test, but two of them, models for UNCER1_2 and 3, do badly for the Hansen test of overidentification.

Table 13 - Estimation Results – Model 2

	(1)	(2)
VARIABLES	rd_intensity	rd_intensity
L.rd_intensity	0.393***	0.303**
	(0.126)	(0.121)
L.uncer1	-0.0153*	
	(0.00917)	
L.uncer2		-0.611*
		(0.369)
L.sale_growth	0.0518	0.114
	(0.0517)	(0.0838)
Constant	-0.275	12.98
	(0.784)	(9.292)
Observations	653	702
Number of firms	60	58
Wald test (p-value)	0	0
AR(2) (p-value)	0.495	0.366
Hansen test (p-value)	1	1

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Notes: The models are estimated using the Arellano-Bond estimator by Arellano and Bond (1991) and implemented by STATA 13 by Roodmand (2009). Robust cluster errors (cluster by firm) are reported in braces. Robust clustered standard errors are implemented by STATA 13 Roger (1994). Year dummies were used in each model. Instrument sets of lagged depend variable (GMM style) and all other right-hand-side variables (IV style). The following tests are applied: 1. The Hansen test as a test of erogeneity and validity of instrument subsets (Since we are using robust clustered standard errors, Sargan test is inappropriate.); 2. AR(2) test as a test for second-order serial correlation, required by suing the Arellano-Bond estimator; 3. The Wald test with the null hypothesis that all the coefficients except the constant are zero. All tests are reported by their p-values for convenience.

Finally, we test the impact of uncertainty on paten, innovation output. The estimation results are reported in Table 6. For this set of estimation, we have the weakest results. None of the uncertainty measures are shown to have significant results for patent output. Even

the impacts of R&D spending and sales growth rate are generally insignificant. The only significant variable across all models is patent stock, which shows significant positive and very consistent impact on patent production across all model. Therefore, from this set of estimation, we only find research capability has significant positive impacts on patent production. This insignificance is consistent with the discussion in the literature. It is mainly due to the complexity of the relationship between uncertainty and innovation output.

Table 14 - Estimation Results-Model 3

	(1)	(2)	(3)	(6)	(7)	(8)	(9)	(12)
VARIABLES	pat	pat	pat	pat	pat	pat	pat	pat
	Poisson RE	Poisson FE	Negative Binomial RE	Negative Binomial FE	Poisson RE	Poisson FE	Negative Binomial RE	Negative Binomial FE
pstock	0.000866***	0.000865***	0.000820***	0.000814***	0.000826***	0.000825***	0.000800***	0.000794***
	(6.17e-05)	(6.18e-05)	(0.000159)	(0.000156)	(7.47e-05)	(7.48e-05)	(0.000149)	(0.000129)
L.uncer1_1	-0.00189*	-0.00184*	-0.00103	-0.000936				
	(0.00109)	(0.00107)	(0.00232)	(0.00187)				
L.uncer2_1					0.107	0.106	0.145	0.132
					(0.156)	(0.156)	(0.298)	(0.284)
L.rd_intensity	-0.00539*	-0.00516**	-0.00351	-0.00318	-0.00388*	-0.00379*	-0.00288	-0.00272
	(0.00279)	(0.00261)	(0.0140)	(0.0157)	(0.00199)	(0.00193)	(0.00514)	(0.00196)
L.sale_real	-4.43e-05***	-4.45e-05***	-3.14e-05**	-3.43e-05**	-4.06e-05***	-4.08e-05***	-2.85e-05**	-3.11e-05**
	(7.72e-06)	(7.66e-06)	(1.30e-05)	(1.34e-05)	(8.63e-06)	(8.58e-06)	(1.22e-05)	(1.24e-05)
Observations	665	662	665	662	732	731	732	731
Number of firms	61	58	61	58	58	57	58	57
Log-likelihood	-5706	-5265	-2824	-2388	-6487	-6057	-3028	-2603
chi2	744.9	204.5	46.61	52.26	690.2	135.1	102	88.77

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1
Note: For each uncertainty measure, the model is estimated using Poisson estimator Random Effect (RE) and Fix Effect (FE), and Negative Binomial Estimator Random Effect (RE) and Fix Effect (FE). Robust cluster errors are reported in braces except for Poisson FE with robust standard errors. All constants are omitted. Log-likelihood test with null hypothesis that some arbitrary group of k coefficients in the model is equal to zero, are applied. The Wald test with null hypothesis that all the coefficients except constant are zeros, are applied.

2.5.3 Summary of Results

To summarize the estimation results, we find that uncertainty has possible negative impacts on investment and R&D spending. The results meet our expectation of the impact and are consistent with relevant literature findings. Lagged effect patterns are statistically confirmed for both investment and R&D spending. However, our estimated impact of uncertainty on patent production is week and ambiguous. Some studies in the uncertainty literature find that large firms are less affected by uncertainty (e.g. Koetse et al., 2006, Ghosal and Yang, 2015). As our sample of firms are all top firms in the pharmaceutical industry, the weak impact of uncertainty is expected.

2.6 Conclusion

Using a panel data of the U.S. and European pharmaceutical firms, we are able to test the effects of uncertainty on firms' investments, R&D expenditure, and innovation performance. The most important contribution of the paper is that this is the first paper to test the effects of uncertainty on the three closely-related variables using the same dataset. Therefore, the estimation results contribute to the debates of the effects of uncertainty on firms' investment decision making and innovation performance, which still don't have conclusive opinions. We find significant negative effects of uncertainty on both investment and R&D spending, but we do not find significant evidence for the impact of uncertainty on patent production.

Our study bears three major limitations. First, we use patent application numbers as the measure for innovation, which is a common practice in the literature. However, due to the fact that patents vary in their value or financial benefits for the firm. Our measure of

innovation is not accurate in the term of innovation product quality. Second, the validity of uncertainty measures we used in the paper are all limited to the method of regression or calculation. We were not able to get a survey-based measure for robustness checks. Finally, our conclusions from studying the dataset of large firms in the pharmaceutical industry cannot be applied to other industries that are not similar to our dataset. Therefore, although our study can contribute to the debates on the effects of uncertainty, the conclusion cannot be generalized. In addition, for the potential "incidental parameters problem" in fixed effect Negative Binomial regression models, we have noticed several options to deal with this type of problem. We will address this potential bias later on.

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CHAPTER 3. MEDICAL DEVICE RECALLS

3.1 Introduction

Medical devices are a critical part of the US economy, equaling roughly 6 percent of total health expenditures (Grennan and Town 2015). They provide lifesaving assistance such as coated arterial stents, MRIs, or defibrillators, or may be a useful part of the medical system that is less complex such as syringes and stethoscopes. When there are defects in such devices, the results can vary in terms of safety impact to people from minimal harm to potentially life threatening.

Devices may be recalled from use because of defects before or after a serious crisis. Recalls are remedial actions that companies take, either voluntarily or under FDA notification, regarding potentially dangerous health risks for medical devices that are either defective or unsafe. A US government General Accounting Office Report (2011) offers a number of potential factors that are associated with for medical device recalls. These include process control, device design, software design, component design/selection, false or misleading labeling, mistaken use of materials or components, and/or employee error. Many of these factors implicate issues within the supply-chain, operations management, organizational management (e.g., regarding compliance, quality control and innovation within the firm) as well as management of various parts of production and delivery across complex supply chains. The FDA data show that the number of medical device recalls have increased over time but so have the number of devices. In terms of the examining the underlying determinants of medical device recalls, the literature is relatively small and much remains unclear about what drives specific devices to be recalled.

This paper makes a number of contributions. First, we seek to examine the firm level determinants that contribute to medical device recalls in the context of product quality. Regulation of medical devices may impact innovation, a point first made by Peltzman's (1974) seminal paper on the FDA in the pharmaceutical context. However, pharmaceutical regulation has a much longer history than medical device regulation and the relationship between the recall regime (Thirumalai and Sinha 2011), and innovation in medical devices (Chatterji (2009), Chatterji and Fabrizio (2015)) remains understudied.

Second, the firm-size and organizational structure of the medical device industry is complex and there is variation as to types of firms that participate in the manufacture of devices. For example, some firms are very large multi-product conglomerates across many industries such as General Electric, Siemens and Phillips. Other firms are multi-product in the broader healthcare industry, and make pharmaceuticals, medical devices, among other products: e.g., Johnson and Johnson. Then there are firms that are primarily medical device firms but large and multi-product, such as Medtronic and Boston Scientific. Finally, there are much smaller firms that produce a single medical device. Given this heterogeneity and context, we add to the literature that examines the economies of scale and scope in production and in the supply-chain among manufacturing firms and related to issues such as product complexity and the amount of vertical integration (for example, Williamson (1985), Hendricks and Singhal (2001), Rawley and Simcoe (2010), Cachon and Terwiesch (2012)).

Third, we focus on firms' financial and economic conditions that may impact medical device recalls. A number of papers analyze issues such as sales, growth and

profitability within the medical device sector. We add to this literature (Thirumalai and Sinha 2011) in the context of medical device recalls.

Fourth, we add to the literature more generally on recalls. Examining medical devices permits us to focus on recalls in a single industry. This adds to existing knowledge on medical device recalls (Thirumalai and Sinha 2011), as well as having potential implications for the study of recalls in other sectors such as toys (Hora, Bapuji, and Roth 2011), and automobiles (Rupp and Taylor 2002; Haunschild and Rhee 2004; Eilert, Jayachandran, Kalaignanam, and Swartz 2017). There are other papers that focus on recalls across multiple industries (Chen, Ganesan, and Liu 2009; Marucheck, Greis, Mena, and Cai 2011; Cleeren, Dekimpe and van Heerde. 2017) and make generalizations, but these may not necessarily hold for the medical device industry.

Finally, to enable a detailed examination of recalls, we have compiled a large and comprehensive dataset which includes data on recalls we hand-collected from the FDA website. The firm-level recall data were then merged with a range of firms' financial and economic data. Based on our substantial dataset, we are able to conduct an extensive analysis of the firm-level determinants of medical device recalls.

In our empirical analysis, our objective is to examine whether there are systematic longer-run differences in recalled devices across the firms in our sample, and whether firm-specific and device-specific attributes can explain the differences. Attempting to parse out these longer-run relationships allows us to examine, for example, whether the systematic differences in firms' R&D spending, extent of vertical integration in components

manufacturing, firm size, complexity of the medical devices, firm's national identity, among other variables, generate higher or lower number of recalls.

The remainder of the paper is organized as follows. In Section 2, we provide a background of the FDA and how it regulates medical devices generally and its processes for medical device recalls. Section 3 provides a discussion about product quality and explains variables that we use to test for relationships and causality for quality on medical device recalls. Next, in Section 4 we go through the empirical specification while in Section 5 we discuss the data and the variables. We offer estimation and results in Section 6 and a discussion and summary of the results in Section 7. Finally, we conclude with policy implications and recommendations in Section 8.

3.2 FDA Institutional Details and Process

The Food and Drug Administration (FDA) is responsible for the regulation of medical devices. [20] Its role in the first stage is to guarantee the "safety and effectiveness" of medical devices via pre-market approval of devices. As part of its pre-market supervision, the FDA classifies medical devices into three classes of products based on the level of risk and the level of pre-market review. Class I devices are those that pose the least risk, Class II devices pose moderate risk, and Class III devices the highest risk to

[20] FDA formally defines a medical device as follows ((Federal Food, Drug, and Cosmetic Act, 2005, Sec. 201 (h), 21 U.S.C. 321): "A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is: recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

patients. An example of a Class I device is a syringe while an example of a Class II is a powered wheelchair. In contrast, an example of a Class III device is a pacemaker (which is implanted into the body). Yet another category of devices are exempt from premarket approval, such as stethoscopes. A number of statutory changes (1997, 2002, and 2007) have occurred to speed up approval times for various medical devices. Since the 1997 changes, the approval time for Class III devices has been reduced (Zinn, Allen, and Hacker 2012).

Even with a significant pre-market approval safeguards, once a device is released to the public there is the possibility that either pre-market approval did not anticipate broader situations in which potential defects for medical devices may emerge or firms may develop quality control and performance problems. The FDA also ensures compliance with broader patient goals and to police against device defects through post-market surveillance such as through inspections. The FDA inspects approximately 3,000 device firms every year.

We summarize critical developments involving the FDA and various milestones in Table 13. Though the first major device aspect of FDA regulation had its origins in the Federal Food, Drug, and Cosmetic (FDC) Act of 1938, which extended control to various therapeutic devices, the modern medical device regulatory regime was born in 1976 with the Medical Device Amendments. The purpose of the amendments was to ensure both the safety and effectiveness of medical devices. The amendments required medical device manufacturers to register with FDA and introduced quality regulation and procedures. It also introduced both pre-market approval and performance standards prior to marketing of the devices.

Table 15 - Some Key Dates in FDA Regulations

Year	Act/Event
1938	Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040
1976	Medical Device Amendments. Pub. L. No. 94-295, 90 Stat. 539 (1976)
1990	Safe Medical Devices Act of 1990; Pub. L. No. 101-629, 104 Stat. 4511 (1990)
1991	Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities; Final Policy; FDA Compliance Policy Guide, 7150.09, 56 Fed. Reg. 46,191 (Sept. 10. 1991)
2002	Medical Device User Fee and Modernization Act, Pub. L. No. 107-250, 116 Stat. 1588 (2002)
2002	Medical Device User Fee and Modernization Act (MDUFMA)
2003	Medical Product Safety Network
2005	Medical Device User Fee Stabilization Act of 2005
2007	Food and Drug Administration Amendments Act of 2007 (FDAAA)
2010	Medical Device Tax as part of Affordable Care Act- Pub. L. No. 111-148, §§ 9009, 10904, 124 Stat. 119, 862, 1016 (2010) (PPACA), as amended by the Health Care and Education Reconciliation Act of 2010, Pub. L. No. 111-152, § 1405, 124 Stat. 1029, 1064 (2010)
2010	FDA Office of Regulatory Affairs, Regulatory Procedures Manual
2011	GAO Report: Medical Devices FDA Should Enhance Its Oversight of Recalls
2011	FDA Report: The Case for Quality
2012	Food and Drug Administration Safety and Innovation Act (FDASIA)
2013	FDA Final Rule Global Unique Device Identification Database (GUDID), 78 FR 58786
2015	GAO Study: FDA Ordered Post-market Studies to Better Understand Safety Issues, and Many Studies Are Ongoing
2015	GAO Study: Medical Devices: FDA Ordered Post-market Studies to Better Understand Safety Issues, and Many Studies Are Ongoing

In 1990, detection of device defects improved with the Safe Medical Devices Act. The act required health care facilities that used medical devices to report incidents of medical device defects to the FDA that might have probably caused or contributed to the death or other serious adverse outcome of a patient. Further, the act required manufacturers to conduct post-market surveillance on permanently implanted devices. In furtherance of the quality aspect of devices, the act authorized the FDA to order medical device recalls.

Further changes to improve the quality of medical devices resulted in the 2002 Medical Device User Fee and Modernization Act. Among other things, it created provisions for medical device inspections by accredited third-parties. It also created

requirements for reprocessed single-use devices. That year, the FDA also launched the Medical Product Safety Network, which is a collaborative reporting program that identifies adverse effects relating to medical devices.

In 2011, in part to respond to increases in the number of devices entering the market and a review of device quality related data regarding manufacturing risks, the FDA launched what it called the Case for Quality in 2011. The case for quality included three core components: a focus on quality, enhanced data transparency and increased stakeholder engagement through improved collaboration. Finally, in 2015 the FDA promulgated the Final Rule Global Unique Device Identification Database (GUDID) to help properly label medical devices in their distribution and use and submit data to the GUDID.

As with many areas of regulation, the FDA outsources much of the day to day compliance to its regulated firms (Ayers and Braithwaite 1992; Kaplow and Shavell, 1994; Toffel and Short 2011). In this context, most detection and regulation of device recalls is voluntary, though the FDA orders some recalls. When there are recalls, the FDA evaluates risk of recall from highest (Class I) to lowest (Class III). There recall class are:

1. Class I: serious adverse health consequences or death;

2. Class II: temporary or reversible adverse health consequences or death; and

3. Class III: minimal health consequences.

A recall is triggered by firm awareness of a defect or other health risk. When a firm becomes aware of a potential defect, it begins a process to investigate the potential defect and to notify the FDA. There is a lag time between the time that firms investigate recalls

until the time they self-report to the FDA. The FDA responds with a classification of the recall. The firm creates a recall strategy at which point the FDA reviews the adequacy of the plan and suggests appropriate changes to the plan. A recall is terminated by the FDA when the FDA determines that reasonable efforts have been made by the manufacturer with regard to the recall. Unlike some consumer products where recalls may occur rapidly, we find that for Class I recalls this average is nearly 8 months.

As the above timeline and process of FDA regulations related to medical devices shows, it has undergone noteworthy changes over the years resulting in intertemporal variations in procedures and recalls. Our data on the total number of recalls shows a clear upward trend over our sample period 2001-2015. There are likely several factors contributing to this. For example, entry of new firms to the industry, changing composition and complexity of devices, and the overall political-economy of the regulatory process. The political economy of device regulation has been studied over time, by Hamburg and Sharfstein (2009) Garber (2010), Kramer, Shauai and Kesselheim (2012), and most recently by Stern (2017). Over time the FDA has made regulatory changes to attempt to promote innovation and bring products to market more rapidly. This has been an evolutionary process and remains relatively understudied relative to a more robust literature on pharmaceutical FDA regulation.

3.3 Modeling Product Quality

In this section we outline an empirical model of the determinants of a firm's product (medical device) quality. The specific approach we take is to consider a firm's product quality production function. Under this approach, the firm's product quality as a

deliverable (or output). We then specify firm-specific inputs and attributes that could influence the firm's product quality.

While we discuss a wide array of variables that may influence product quality, due to some data limitations we note later, in this paper we are unable to include the full set of device-specific characteristics. The extensions of this paper will include those characteristics.

Potential factors that may be inputs into a firm's product (medical device) quality may include:

(1) Innovation expenditures (*R&D*). The literature on innovation in medical devices is considerably smaller than that of pharmaceuticals (Thirumalai, and Sinha 2011; Goldman and Lakdawalla 2012; Stern 2017). [21] The prior literature shows that there are some differences between innovation in pharmaceuticals and medical devices. Medical devices tend to have a shorter innovation process and smaller firms exhibit less entry than pharmaceuticals. R&D does play an important role in the medical device industry. Approximately 9-11 percent of revenue in device companies is spent on R&D while for smaller device firms (those with $5 million or less in revenues), the average R&D expenditure is 343 percent of revenues (Chatterji, Fabrizio, Mitchell and Schulman 2008).

Product quality is often used to measure R&D success (Harter, Krishnan and Slaughter 2000, Eggers (2014). We suggest that higher R&D expenditures by a firm are

[21] There is a broader literature on medical devices but it tends not to on the issues involving recalls and their relationship to innovation. See Chatterji (2009), Garber (2010), Zuckerman, Brown and Nissen (2011), Chatterji and Fabrizio (2015).

expected to contribute to higher product quality (lower recalls) for medical devices. High value components require more R&D intensity as these components are the ones more likely to command higher margins because of quality differentiated products (Pisano and Teece 2007).[22]

(2) Firm size (*Size*). Firm size may matter, but there are countervailing forces and this implies that the net effect is ambiguous. Larger firms may have a variety of organizational, incentive, compliance, and other problems that may negatively affect delivery of quality. Firms benefit from increased economies of scale as the cost of production reduce per unit. However, there reaches a point at which various costs of organization and agency costs mount which reduces the efficiency of scale. That is, organizational complexity may dictate diseconomies of scale that create inefficiencies in ownership (Williamson 1985). For some firms, organizational complexity creates diseconomies of scale for which smaller firms are better to address agency cost problems than larger ones (Zenger 1994; Hendricks and Singhal 2001; Shaver and Mezias 2009). Likewise, larger firms, with its layers of bureaucracy may be more prone to inertia (Miller and Chen 1994).

Another strand of literature suggests that firm size may positively relate to firm innovation (Damanpour 1992). Typically, smaller firms tend to be better suited to exploit product innovations due to specialized technological knowledge. This is due in part to more layers of hierarchy at larger firms, and more rigidity regarding changes that otherwise may lead to significant new types of innovation. In contrast, larger firms are more effective

[22] We note however that new processes may create disruptions in learning routines, as explored by Hatch and Mowrey (1998).

at process related innovations (Yang, Zheng and Zhao 2012). Large firms are able to leverage their specialized knowledge and routines via learning by doing to address more complex processes (Winter 2003).

Quality is an important aspect that emerges from firm learning such as through quality control and total quality management programs (Li and Rajagopalan 1998; Iyer, Saranga and Seshadri 2013). This may suggest a case for larger firms delivering higher quality. Larger firms may have more to lose in terms of reputation, etc., and may try to be more conscious about quality and reputation.

Firm size also implicates the literature on economies of scope. To the extent that larger firms develop economies of scope, the scope economies may allow for greater productivity of existing manufacturing. [23] A large firm can utilize its scope in R&D, distribution channels and marketing across a number of different products more efficiently than a single product smaller firm (Cachon and Terwiesch 2012). However, a firm with too many product lines many create inefficiencies in management based on overly broad scope (Rawley and Simcoe 2010).

(3) Sales growth (*Growth*). This variable measures a firm's overall sales growth across all product lines and not just the recalled medical device. Faster firm-wide sales growth (overall expansion) may contribute to difficulties in components supply-chains coordination, quality assurance, and maintenance of quality standards. Certainly, based on prior research of firms that can be classified as high-growth, when such firms issue product

[23] However, recent work by Brahm, Tarzijan and Singer (2017) suggests that scope economies may encounter frictions that reduce productivity such that there is an inverted U relationship regarding efficiency and product variety. In other work Zhou and Wang (2017) find that there are trade-offs involving scope and scale economies in complex supply chain systems.

recalls, this results in a significant negative stock impact (Hendricks & Singhal, 2003, Thirumalai & Sinha, 2011). Faster growing firms may have trouble delivering higher quality because of issues of scaling production up too quickly without proper quality control systems in place (Zook 2016). As a result, faster growth may adversely affect maintaining quality and other standards.

(4) Profitability (*Profits*). Higher profitability is expected to contribute to higher quality delivery as firms have the financial ability to invest in better process and product management, innovation, and quality assurance. However, findings regarding profitability and innovation are mixed (Rosenbusch, Brinckman and Bausch 2011). Some papers find positive effects[24] and some negative effects.[25]

The relationship between profitability and recalls may not be clear. One might imagine because of stock market effects due to direct costs and reputation, it is not clear which way that firms might respond with regard to compliance and quality systems. Firms that choose short-term profitability might invest less in quality than firms that are more concerned about long-term profitability and reputation effects.

(5) Degree of vertical integration (*Integrate*). An important aspect of a firm's production structure is the degree of vertical integration for components production. Some firms can have large in-house parts manufacturing, whereas other firms subcontract extensively and maintain close collaboration with suppliers. The literature suggests that firms with superior capabilities in subcontracting components manufacturing and

[24] McGee, Dowling and Megginson (1995) for example.
[25] Li and Atuahene-Gima (2002) for example.

coordination can increase product quality and procurement efficiencies.[26] The overall set of characteristics related to supply-chains, procurement and coordination, however, are extremely difficult to measure.[27] We follow Lieberman and Dhawan (2005) in creating a proxy measure: they use a firm's "value-added" as a proportion of sales (Integrate) as a measure of vertical integration. Higher values of Integrate implies less reliance on suppliers and a greater percentage of in-house components production.[28] Based on this literature, we expect higher Integrate to be related to potentially lower product quality on average.[29]

(6) Product Complexity (*Complex*). The more complex a product, delivering quality, on average, will be costlier and difficult. The literature on supply chain management suggests that a product that requires more components and more significant component interaction creates more product complexity (Novak and Eppinger 2001). Such complexity requires more coordination and therefore may increases costs. Thus, the more severe the defect, the more complex the fix may be for the medical device given the complexity of the device. In our analysis, we use two variables to measure whether a device is complex: (a) is the device implantable or not; and (b) the device class. We discuss these measures in more detail in our data section.

[26] Helper and Sako (1995), Dyer (1996), Womack et al. (1990) and Lieberman and Dhawan (2005), for example, study these aspects for the automotive manufacturing by comparing strategies by the U.S. and Japanese producers in attaining product quality and production efficiencies. They show that the extensive components outsourcing model of the Japanese firms generated more efficient and higher quality outcomes.
[27] The empirical literature on the benefits for outsourcing is mixed. Compare for example Rothaermel, Hitt and Jobe (2006) and Mols (2010).
[28] As in Lieberman and Dhawan, this measure allows a test of the relative value of integration versus subcontracting.
[29] As noted by Lieberman and Dhawan (2005), the ratio of value-added to sales is not an indicator of the coordination aspects between the manufacturer and the components provider, which is clearly very important in assessing the totality of the subcontracting and coordination picture. In this sense the value-added to sales ratio provides a relatively basic control variable.

(7) Time from device approval to recall (*InMarket*). One might hypothesize that the longer a device has been on the market, the more likely it is that any defects are detected, and the device potentially recalled. Since FDA approval and the amount of trials necessary may vary across devices, those devices that do not have significant clinical trials may not have the level of exposure to allow for defects to make themselves be revealed. Therefore, more time on the market allows for the possibility of reducing the information gap regarding defects.[30] However, the marketing literature suggests that the time to recall a project is related to the severity of the problems. The more severe the problem, the larger the time to recall in automobiles (Eilert, Jayachandran, Kalaignanam, and Swartz 2017). Like automobiles, defects in medical devices may not always be detected rapidly. Also like automobiles, many device companies produce a series of products. The same authors find that in increase in scope of products increases the time to recall.

(8) Recalled medical device sales (*DeviceSales*). This argument is similar in spirit to InMarket. The more are the number of units of the specific device sold, the more likely it is that any defects are detected and the device potentially recalled. However, the size of the recall may delay the recall because of the complexity of having to manage the recall of additional units (Eilert, Jayachandran, Kalaignanam, and Swartz 2017).

(9) Firm Type (*Type*). Does the firm make medical devices only, or does it produce devices as part of the firm's broader multi-product operations spanning across industries? A firm that is specializing in devices only is likely to be better able to control for various

[30] Dasgupta and Xie (2017) suggest the management issues generally that arise in recall situations is a trade-off between how precise the knowledge is about a potential defect on the one hand versus waiting for more information and risking a costlier recall that also may result in injury or death on the other hand.

process, compliance and operations, supply chains, and deliver better quality (fewer recalls). Thirumalai & Sinha (2011) find that a greater product scope makes medical device recalls more likely. However, no work on medical devices examines firm type in terms of scope as say between recalls for a conglomerate firm such as General Electric and a multiproduct device firm such as Medtronic.

(10) Nationality (*US*). The nationality variable could potentially proxy for multiple characteristics. First, U.S. headquartered firms may potentially be in a better position to understand U.S. FDA regulatory processes and approvals standards. Across jurisdictions there are different regulatory standards and differences in quality control. Steven, Dong and Corsi (2014) find that offshore outsourcing is more likely to have quality problems than outsourcing domestically. Similarly, in work regarding compliance and corporate governance, family firms are less willing to list (and be subject to more stringent regulation) in jurisdictions where compliance standards are stronger (Saudagaran and Biddle 1995; Chung, Cho, and Kim (2015)). If this is so, then U.S. firms would be less likely to have recalls. A counter to this argument is that many of the foreign firms have significant operations in the US. If this is so, then it is less clear whether US firms have an advantage. Within the compliance relating to corporate governance and securities compliance Reese & Weisbach (2002) and Doidge, Karolyi and Stulz (2004) suggest a bonding hypothesis that foreign firms will list in the United States as a way to have higher standards. Further, U.S. firms on average may have different organizational structures, corporate cultures and compliance mechanisms compared to foreign firms. The US variable would help proxy for these aspects.

Considering medical device quality as an output, and the various inputs and attributes noted above, we have a product-quality production function. Our dependent variable is product recalls, which is the inverse (negative) of quality. Our control variables are 1-10 noted above. In our sample, all firms have at least one device recall over our sample period.[31]

$$Recalls_i = A_i \cdot \boldsymbol{Z_i} \cdot \epsilon_i \tag{14}$$

In specification (14), the dependent variable, $Recalls_i$, is the number of recalled devices for the firm, the subscript i denotes firm, $\boldsymbol{Z_i}$ is the vector of variables 1-10 described above, and ϵ_i is the error term (we discuss the characteristics of the error term in more detail in the next section). The term A_i represents the unobserved firm-specific overall technology by which the firm converts various resources and attributes to delivering product quality.

As we noted earlier in this section, due to some data limitations we note later, in this paper we are unable to include the full set of device-specific characteristics. The extensions of this paper will include those characteristics.

3.4 Empirical Specification

[31] Our data only cover those firms that had devices recalled. Our data do not include firms with zero recalls. Creating a dataset that is encompassing and includes all firms selling medical devices in the US is beyond the scope of our study as it entails identifying all US and foreign firms selling devices in the US. Prior studies such as Thirumalia and Sinha (2011) also have samples containing only those firms that have positive recalls.

Our objective is to examine whether there are systematic longer-run differences in recalled devices across the firms in our sample, and whether firm-specific and device-specific attributes can explain the differences. Attempting to parse out these longer-run relationships allows us to examine, for example, whether the systematic differences in firms' R&D spending, or extent of sub-contracting components, or firm size, among other variables, generate higher or lower number of recalls. In this sense, specification (14) allows us to examine how the variables in $\boldsymbol{Z_i}$ affect recalls.

As our estimation is for a cross-section of firms, to go from specification (14) to a cross-firm regression, we specify $A_i = A + \eta_i$ where A reflects the "common elements" across the firms of the technology by which firms deliver medical device quality, and η_i the idiosyncratic firm-specific component.

In specification (14), therefore, the error term is modeled as: $\epsilon_i = \upsilon_i + \eta_i$. The term η_i is the firm-specific idiosyncratic component noted above. The term υ_i includes any other omitted (from the specification) factors that influence a firm's delivery of product quality. The elements of υ_i are firm-specific and could, for example, include a firm's attributes related to overall organizational structure, legal and regulatory compliance structures and mechanisms, unobserved aspects of a firm's supply-chain, among others. In our analysis, some of these firm-specific elements are unmeasured as we do not have any variables to proxy these aspects. Having said this, we do have variables included in our model, like *Type*, *Size*, *Integrate*, and *US*, among others which indirectly proxy for some of these aspects. With the above issues in mind, we *log-linearize* (14) and estimate a cross-section specification.

3.5 Data and Variables

The FDA enforcement reports provide announcements on medical device recalls covering Class I, II, and III recalls and collects various information about the recalled device and firm. We collected data from the FDA Medical Device Recalls database.[32] The database contains FDA Medical Device Recalls since 2001. This database is a collection of the weekly FDA Enforcement Reports. Information collected for the Enforcement Reports includes the class of the recall, the product name, product code, whether or not the device is in vitro, the PMA/510(K) Number, the recall date, recall number, reason for the recall, recalling firm and the root cause of the recall. The information was collected for class I recalls starting 2001 and up to 2013.[33] The actual total number of recalls is smaller than those reported by the Enforcement Reports because they count as separate recalls multiple product recalls from the same firm on the same day. These are products from the same product line. Put differently, the FDA recall data is poorly organized (does not easily identify products from the same product line so that it seems like there are multiple products being recalled – this reduces recall numbers by roughly ¼). Overall, there are 315 recall records in Class I recall dataset for the period 2001 to 2013. There are 258 unique firm names in the Class I recall data. We collapse these multiple entries into one recall, as per Thirumalai and Sinha (2011).

[32] See https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRES/res.cfm.
[33] The database does not contain information on class 1 recalls for 2002, but contain data for 2001 and then for 2003 onwards.

Data on the number of medical devices recalled[34], Complex, InMarket, and DeviceSales were compiled from the FDA database.

(a) We proxy device complexity, Complex, by two variables from the FDA database:

(i) Implantable device ($Complex^{Implant}$). Implantable device is a subset of devices that are specific to something that are implanted in the body. The assumption is that devices that are implanted are on average more complex, likely require a high degree of sophistication and product quality, and failures can be significantly detrimental to a patient's health. Implant is entered as a dummy variable where Implant=1 if the device is implantable, and =0 otherwise; and

(ii) Device class ($Complex^{DeviceClass}$). This is a contributing factor to a device's complexity. The device class can be I, II or III. Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. For example, syringes are classified as Class I devices. Class II devices are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device's safety and effectiveness. For example, powered wheelchairs are classified as Class II devices. Class III devices are generally the highest risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed. For example, replacement heart valves are classified as Class III devices.

[34] Ideally, we would like to have the number of recalls scaled by a size variable, such as the number of products. Therefore, the correlation between the number of recalls and DeviceSales can be restricted to show only the true effect except the effect from firm size or sale. However, given the size and diversity of the firms, it is not possible to get data on the number of products the firm makes.

(b) To calculate the time a recalled device has been in the market, InMarket, we use data on the date the device was approved to the date it was recalled, measured in the number of years (each month is denoted by 1/12).

(c) Number of units sold (sales volume) of the recalled device, DeviceSales. These sales occur during the period the eventually recalled device was sold in the market.

As we are conducting an empirical analysis of product recalls and need economic and financial data, we focus only on the publicly traded firms both U.S. and foreign. Our financial data are from Compustat, including both Compustat North America and Compustat Global. While many firms subject to device recalls are private, there is no systematic way of obtaining the necessary economic data on those firms.[35] After dropping these firms, we have 166 firms (including both parents and subsidiaries) left in our sample.[36] These firms either have or belong to firms with financial data in Compustat. These 166 firms belong to 71 parent firms. After dropping 4 more firms[37], we finally have 67 parent firms with financial data from Compustat in our sample. The related recall data we use are associated with 212 of the total 315 Class I recall records available from the FDA.[38]

[35] Other papers in the literature such as Thirumalai and Sinha (2011) also consider publicly traded firms in their analysis.
[36] As noted earlier, there are 258 unique firm names in the Class I recall data.
[37] The reason for dropping these firms include: (1) the firm was acquired by or merged into another firm before 2000, the beginning of our sample period; (2) the firm has many unusual values and only started during the late part of our sample period.
[38] We offer the following summary of our data. There are a total of 315 Class I recall records with 258 unique firm names (both parent and subsidiary firms). We identify the parent firms using the ownership relation data from MergentOnline (Bloomberg as reference for ownership changes). From this we obtain a total of 71 "parent" firms with financial data in Compustat (166 of the 258 firms). We then drop 4 firms due to M&A or data anomalies. The final sample contains 67 firms, which are associated with 212 of the 315 recall records.

We matched the recall data with Compustat financial data 2001-2015. The data on firm-level R&D, Size, Growth, and Profits are from the Compustat North-America and Global. The variables are:

(a) As is standard in the literature, we measure R&D as R&D-intensity: the ratio of R&D expenditures to sales.

(b) We use the commonly used measure for firm size: the number of employees.

(c) We use a measure of profitability: net profit margin defined as follows: $Net\ profit\ margin = \left[\frac{Net\ income}{Sales\ revenue}\right]$.[39] As some of our firms are foreign and their equities traded in foreign exchanges, we were unable to get their stock prices.

(d) Real sales growth, measured as the average annual rate of growth of real sales.

(e) Following Lieberman and Dhawan (2005), we use a measure of vertical integration, measured as the ratio of value-added to sales.

To measure the type of firm, Type, we used information on each firm's primary and secondary SIC codes. We classify three types of firms:

(i) Type 1 are firms that only make medical devices (e.g., Boston Scientific, Medtronic). We label these firms $Type^{Devices}$ =1 if the firm is devices only, and =0 otherwise;

[39] The net profit margin measures the percent of sales revenue that a firm can eventually keep as its net profit.

(ii) Type 2 are firms that are in the broader healthcare industry which make devices but also pharmaceuticals and related products (e.g., Abbott, Johnson & Johnson). We label these firms as $Type^{Healthcare}$ =1 if the firm is in devices and broader healthcare, and =0 otherwise; and

(iii) Type 3 are firms that are multi-product conglomerates producing a wide range of products outside of the healthcare area (e.g., General Electric, Siemens, and Phillips). We label these firms as $Type^{Conglomerate}$ =1 if the firm is a conglomerate, and =0 otherwise.

As there are three Type dummies, in the estimated regression we enter two dummies.

Finally, we examined where the firm was headquartered. We created a dummy variable *US* =1 if the firm was headquartered in the U.S., and =0 otherwise.

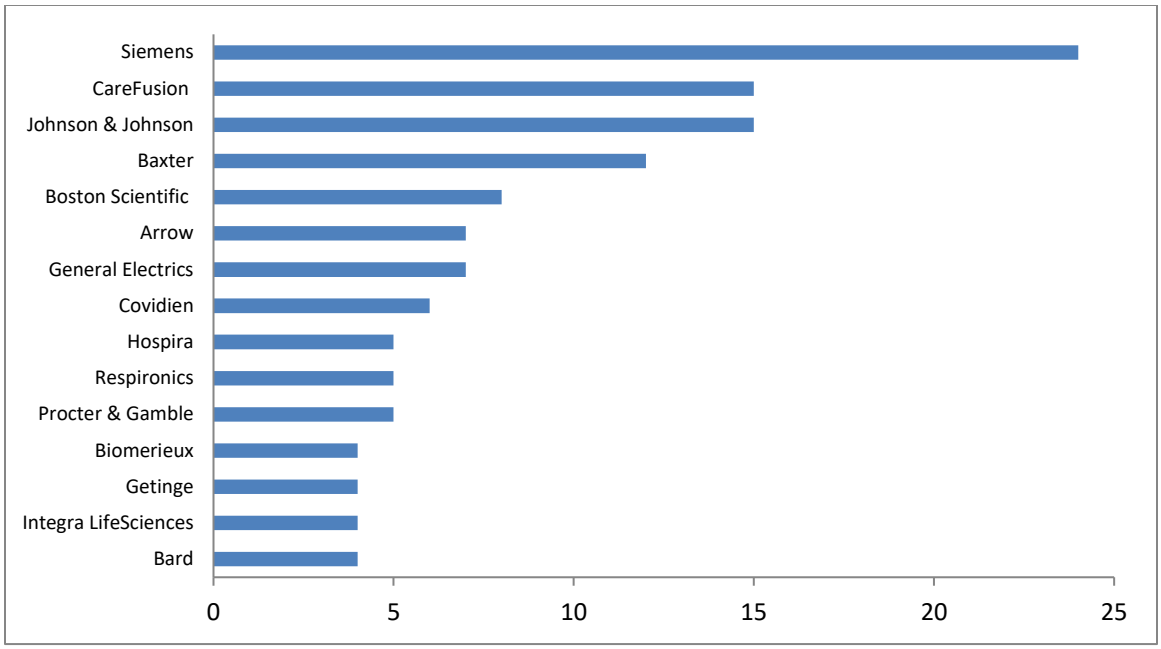

Figure 6 - Top 15 firms with the most recalled devices

Notes: The figure shows the total number of recalled devices over our sample period for each firm.

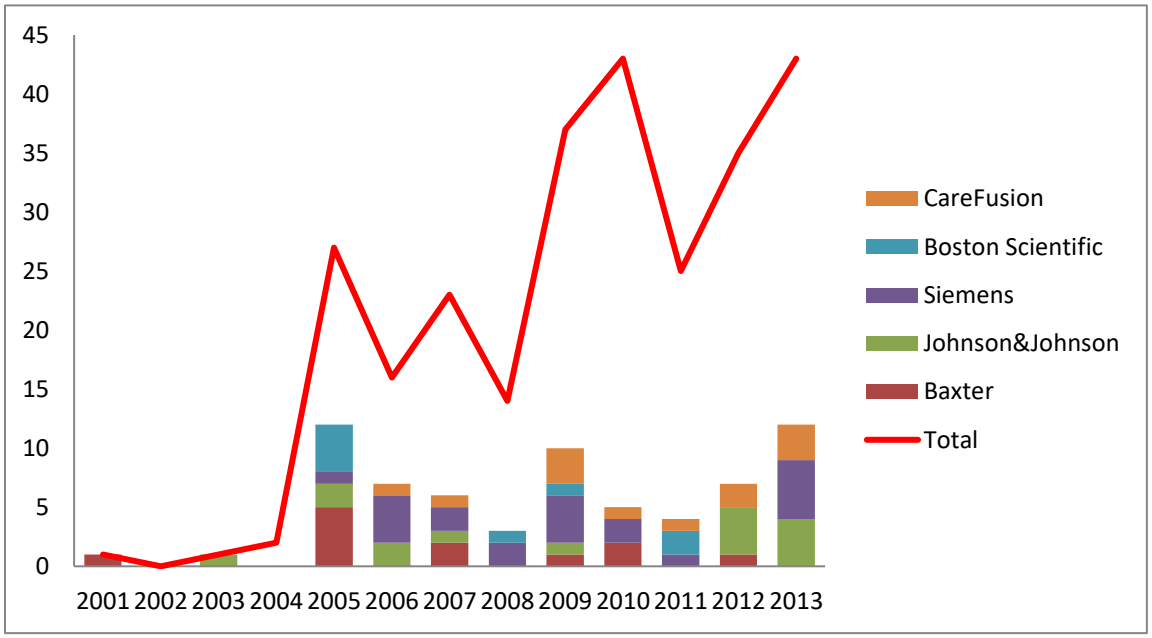

Figure 7 - Total trend of recalled devices and the proportion of top 5

Notes: The red line shows the total number of Class I recalls per year. The bar chart is based on the top-5 firms in figure 1 and their recalled devices per year.

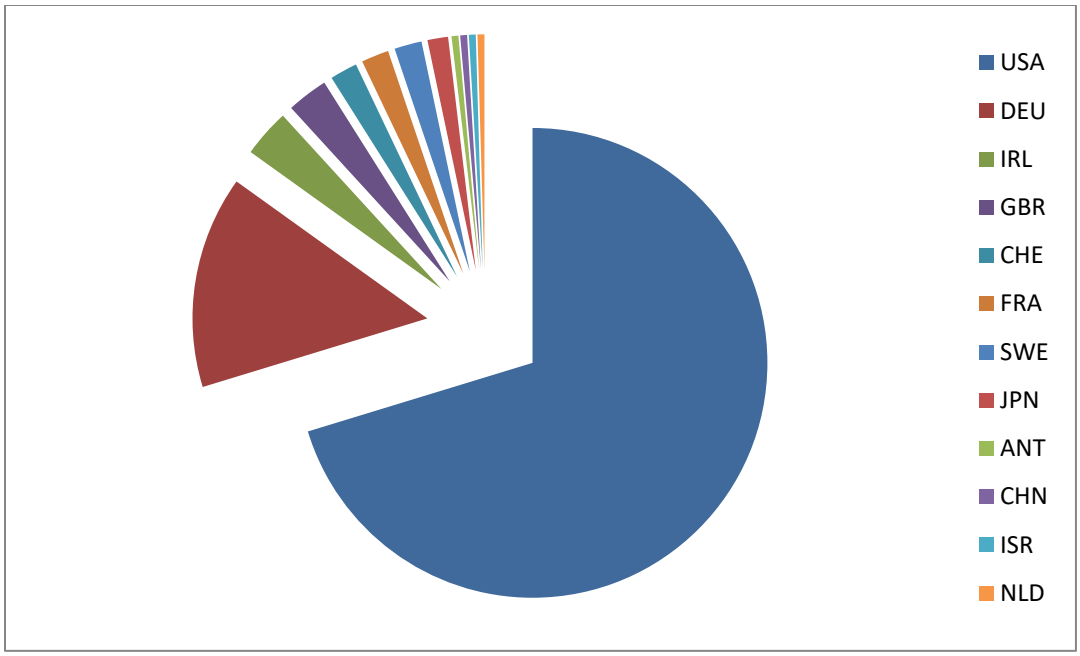

Figure 8 - Total number of recalled devices by country

Notes: Based on the headquarters of the company.

In Figures 6-8 we display some of the data. Figure 1 shows the top-15 firms with the most recalled devices. The top five contain a fairly wide mix of firms, including a giant multinational and multiproduct conglomerate like Siemens (the firm with the largest number of recalls), a medical devices specialty firm like Boston Scientific, and a broad-based healthcare provider like Johnson and Johnson. In Figure 2 we show the composition of firms by nationality/headquarters. The US-firms have the largest share, but the US firms also dominate the number of firms in the sample. Next highest are firms of German origin. Finally, in Figure 3, we display the total number of recalls per year, and the shares of those recalls by the top-5 firms. The total number of recalls show a clear trend, but the distribution of those recalls by firm vary considerably across the years. For example, the

data for Siemens, which has the highest number of recalls over the sample period, shows wide variation in the number of recalls per year over the sample period.

Next, in Table 14, we present the summary statistics for the variables in our model. The main takeaway from the summary statistics is that there is large cross-firm variation in the data, both in the dependent variable (number of recalls) as well as the likely economic and device-specific determinants.

Table 16 - Summary Statistics

Variable	Mean	Std. Deviation
Recalls	3.12	3.96
In Market	7.82	7.01
Devices Sales	933,175.00	4,040,860.45
R&D Intensity	0.10	0.11
Firm Size	31.88	68.32
Net Profit Margin	-0.05	0.53
Vertical Integration	0.39	0.32
Complex (Implant)	na	na
Complex (Device Class)	na	na

Notes:
1. All income or spending variables are in millions. The firm size variable is in thousands.
2. Recalls are the total number of Class I recalls over the sample period.
3. "In Market" is the number of years that the device has been in the market until it is recalled.
4. "Devices Sales" are the actual number of units of the eventually recalled device that were sold.
5. "R&D Intensity" is the ratio of R&D expenditure to sales.
6. "Firm Size" is the number of employees (in thousands).
7. "Net Profit Margin" is the ratio of net income to sales revenue.
8. "Vertical Integration" is a measure of firms' vertical integration constructed as the ratio of value-added to real sales.

** As noted in the paper, data on these two variables are incomplete at this time. These are left for future extensions of this paper. The dissertation chapter will cover only those variables noted above for which we have full information.*

9. Complex (Implant) are numerical coding for whether the device is implantable or not.
10. Complex (Device Class) is the dummy variable for the FDA classification of the device based on risk.

3.6 Estimation and Results

Our estimation results are presented in table 3. As we noted in the beginning of section 3, while we consider a wide array of variables that may influence product quality, due to some data limitations we are unable to include the full set of device-specific characteristics related to the complexity of the devices. In future extensions of this paper will include those characteristics.

In table 3, in column A we estimate a baseline specification with the number of recalls regressed on R&D, firm size, net profit margins, and vertical integration. In column B we augment the specification by including a dummy for whether the firm is headquartered in the US or not. In columns C and D we add two device-specific variables: "Device Sales" – measuring the number of (eventually recalled) devices that were sold; and In Market – measuring the number of years and months the (eventually recalled) device was in the market. In column C we enter these two variables by themselves, whereas in column D we also enter an interaction term – the rational being that the combination of time and sales may be a better indicator for any flaws in a device to emerge and get reported. Finally, in column E we add a dummy variable for "Firm Type": this takes value 1 if the firm is a dedicated devices firm, and 0 otherwise. As noted in section 3, this serves as an added control for unobserved firm-specific characteristics.

Table 17 - Estimation Results

Dependent variable: Number of Recalls

	A	B	C	D	E
Intercept	0.547 (0.677)	0.084 (0.640)	0.185 (0.578)	0.330 (0.639)	0.059 (0.756
R&D Intensity	-0.015 (0.152)	-0.035 (0.143)	-0.048 (0.147)	0.087 (0.144)	0.055 (0.154)
Firm Size	0.162*** (0.065)	0.182*** (0.062)	0.142*** (0.051)	0.129*** (0.049)	0.136*** (0.048)
Net Profit Margin	0.069 (0.634)	0.334 (0.362)	-0.244 (0.177)	0.070 (0.569)	0.025 (0.541)
Vertical Integration	0.168 (0.427)	0.059 (0.412)	0.219 (0.341)	0.227 (0.337)	0.164 (0.354)
US HQ Dummy	-	0.391* (0.223)	0.169 (0.223)	0.181 (0.217)	0.202 (0.257)
In Market	-	-	0.117 (0.089)	-0.212 (0.193)	-0.200 (0.181)
Device Sales	-	-	0.076*** (0.028)	0.024 (0.034)	0.029 (0.033)
InMarket*DeviceSales	-	-	-	0.039* (0.022)	0.037* (0.022)
Firm Type	-	-	-	-	0.172 (0.202)
Adj-R^2	0.1807	0.2097	0.2935	0.3007	0.2946
N	52	52	52	52	52

Notes:

1. For variable definitions, see table 2.
2. Firm Type is a dummy that equals 1 if the firm is a dedicated medical devices firm.
3. The following variables are measures in logarithms: Recalls (dependent variable); R&D Intensity; Firm Size; Vertical Integration; In Market; and Device Sales. Net profit margin is not in logarithms as for some firms it takes negative values.
4. Heteroscedasticity-consistent standard errors are in parentheses. The asterisks *, **, and ***, represent significance at the 10%, 5%, and 1% levels, respectively.
5. The total number of firms in the sample is 67. For the device-specific attributes related to "In Market" and "Device Sales" there are missing values resulting in 15 firms from being dropped from the regression. This results in a sample size of 52 firms.

The main findings from table 3, and across columns A-E, are as follows:

(1) Firm size positively affects the number of recalls, with the estimated coefficients being significant at the 1% level. Among the economic and financial variables, this is the only result that is consistent across the various columns. Based on our discussion in section 3, one potential reason for this finding could be that larger firms may have a variety of organizational, incentive, compliance, and other problems that may negatively affect delivery of quality.

(2) R&D intensity coefficients are insignificant in all the columns. At face value, variation in R&D intensities across the firms in our sample does not appear to affect medical device product quality. The base level of R&D expenditures and intensity is quite high for all of the firms manufacturing medical devices, so it may well be the case that the variations across the firms, while quantitatively important, do not appear to matter much for the devices quality control.

(3) Firms' profit margin coefficients are all statistically insignificant. The variable was included to assess whether variation in profitability may affect product quality, with the potential for firms with greater profitability having more resources to invest in quality. This argument is not supported in our data. One plausible consideration is that relatively newer and smaller devices firms often are not profitable for many years, but this does not necessarily imply that their incentives to maintain high product quality is any lesser than more mature and profitable firms.

(4) The measure of vertical integration is not significant in explaining differences across firms in the number of recalls. This result implies that even though there are

considerable differences across the firms in the extent to which they outsource their components, this feature does not appear to be important in devices recalls.

(5) Firms that are headquartered in the U.S. have greater number of recalls on average compared to their foreign counterparts, but the coefficients are not significant at conventional levels.

(6) Finally, we turn to the two variables specific to the devices: their sales, and the extent of time they were in the market before being recalled. Time in market is not significant. However, the number of devices sold is positive and significant. One explanation for this is that as more devices are sold, it allows for any problems to surface, potentially leading to recalls. We also interacted the time in market variable to devices sales. When we do this, both the time in market and device sales variables are insignificant, but the interaction term is positive and significant at the 10% level. Adding the interaction term does not materially add to our understanding of the process, other than reinforcing the view that a combination of time in market along with number of devices sold leading to potential quality issues coming to the surface.

(7) The last variable we add to the model is Firm Type: this is a dummy that takes a value of 1 if the firm is primarily medical devices. This coefficient is insignificant, and does not material alter our other inferences.

3.7 Concluding Remarks

Our exploratory analysis appears to indicate that the economic and financial variables do not matter much in explaining variation in medical device recalls across the

firms in our sample. The two variables that are useful in explaining differences in recalls are firm size, and the number of devices sold in the market (before they are eventually recalled). Both are positively related to recalls. The firm size affect likely arises from a variety of organizational, incentive, compliance, and other problems that may negatively affect delivery of quality in relatively larger firms. The device sales effect could be arising from the fact that as more devices (with hidden problems) enter the market, the problems surface later. Our findings are robust with including of w wide range of potential economics and device specific variables, as well as controls for whether the firm is U.S. headquartered or not, and whether the firm is primarily a medical devices firm or not.

Our future work in this area involves collecting a comprehensive data set on the complexity of the medical devices. We included two variables in our discussion of product quality: whether the device is implantable or not; and whether the device is rated higher in the risk class or not. Once we complete collection of these data, we will be able to better examine whether these two variables explain cross-firm variation in devices recalls, and whether the inferences regarding firm size, device sales, and other economic effects hold. Therefore, the relation between the explanatory variables and the number of recalls will become clearer. With more complete models, as well as more complex interaction terms between the variables, the insignificant results could be improved or better explained. In addition, with more complete data, we can also explore panel data models to investigate more questions. For example, using the number of recalls as the independent variable to explain other variables, such as innovation output.

Based on our exploratory study, we also suggest that the FDA do more to improve systematization of the devices recalls data, in particular those data and information related

to the unique characteristics of the devices. We also think that there needs to be better monitoring and better coordination between regulated firms and the FDA. Given the economic size of the industry, and the healthcare costs imposed by faulty devices, the welfare gains could be large from analysis of more detailed device specific characteristics and recalls. Such detailed data will help us better understand the delay from the time of uncovering of problem till the time the FDA is alerted, as well as issues like how much of this is due to human error and supply chain management rather than technology or gaps in FDA oversight and processes.

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